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EFFECTS OF SEPSIS PROTOCOLS ON HEALTH OUTCOMES OF ADULT PATIENTS WITH SEPSIS

by

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ABSTRACT

Sepsis is a condition that arises from the host's own exaggerated response to an infection, directed towards pathogens, but causing multiple organ failure. Sepsis is one of the most common causes of death, and a considerable absorber of healthcare resources. This frequently fatal condition, despite progress in technology and improving knowledge of pathophysiology, is still poorly understood, carries high mortality and morbidity rates, and survivors are often left with permanent disabilities and poor health outcomes.

Initial presentation of sepsis is often nonspecific, making diagnosis difficult, and causing lifesaving treatment delays. Sepsis guidelines are derived from emerging evidence-based research. While there is a general consensus that the optimal approach to sepsis management is early recognition and rapid intervention, evidence supporting treatment guidelines is evolving and inconsistent. A mandatory quality improvement measure to implement Sepsis Early Management Bundle (SEP-1) went into effect on October 1, 2015, in the settings utilized for this project. An evidence-based project was conducted to evaluate the interventions and the effectiveness of the sepsis protocol on patients' health outcomes and assess whether implementation of the protocol reflected in reduced hospital length of stay, decreased mortality, morbidity, antibiotics utilization and rehospitalizations in a community hospital in the coastal region of South Carolina. A 19-month data collection, retrospective review, and data analysis included 158 participants in two groups, pre-and post-implementation of the protocol.

Results showed that mortality and hospital stay were considerably reduced after the protocols were implemented; however, readmission rates increased, and morbidity increased. Implementing the mandated protocol actually did not uniformly influence the efficiency of interventions. Results of this study can be used to validate the need for improvement and recommend innovative approaches to therapeutic and diagnostic methods that could facilitate earlier and more targeted interventions.

Future studies are needed to identify approaches that can help sepsis survivors to regain independence, return to prior living arrangements, and avoid rehospitalization. Measures of sepsis guideline effectiveness should focus on not only immediate results and mortality rates, but also return to function and long-term effects affecting survivors.

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LIST OF ABBREVIATIONS

AAT ……...Appropriate Antibiotic Therapy

ARISE …….Australasian Resuscitation in Sepsis Evaluation

CMS ……Center for Medicare and Medicaid Services

CVP ……..……...Central Venous Pressure

DIC ……..…… Disseminated Intravascular Coagulation

ED …….…..Emergency Department

EGDT …….Early Goal Directed Therapy

IV……..……... Intravenous

ICU …….....……Intensive Care Unit

LOS ……...……Length of stay

MAP ……Mean Arterial Pressure

NQF ……..……. National Quality Forum

PCR …….…….Polymerase Chain Reaction

ProCESS ……Protocol-based Care for Early Septic Shock

ProMISe …….....Protocolised Management in Sepsis

RCT ……Randomized Controlled Trial

SIRS ……..……Systemic Inflammatory Response Syndrome

SSC …… Survival Sepsis Campaign

$ScvO_2$ …….....……Central Venous Oxygen Saturation

CHAPTER I

INTRODUCTION

Sepsis, also known as blood poisoning, is a common, debilitating, and potentially deadly medical condition. The word *sepsis* is derived from the ancient Greek word for rotten flesh, decay, and putrefaction (Marik, 2014). Although clinical criteria that define sepsis remain controversial, the term refers to the systemic inflammatory response following microbial infection with the presence of some degree of organ dysfunction (Vincent, Opal, Marshall, & Tracey, 2013).

Background and Significance

Defined as a whole body inflammatory response to an infection (Bone, 1992), it is a serious widespread systemic overreaction. Sepsis is more common than heart attack, and claims more lives than any cancer (World Sepsis Day, 2015). It can rapidly progress to a substantial acute organ dysfunction known as severe sepsis, and by triggering a cascade of mechanisms can lead to septic shock, multi-organ failure, and death. Septic shock is associated with overwhelming infection, usually by gram-negative bacteria, although it may be produced by other bacteria, viruses, fungi, and protozoa. It is thought to result from the action of endotoxins or other products of the infectious agent on the vascular system causing large volumes of blood to be sequestered in the capillaries and veins; activation of the complement and kinin systems and the release of histamine, cytokines, prostaglandins, and other mediators may be involved (Farlex Partner Medical

Dictionary, 2012). Clinical characteristics of sepsis include initial chills and fever, warm flushed skin, increased cardiac output and hypotension, and specific inflammatory parameters; if therapy is ineffective, it may progress to the clinical picture associated with septic shock (Farlex Partner Medical Dictionary, 2012).

This condition carries a high mortality rate and a positive outcome depends on early recognition, timely diagnosis, and prompt implementation of aggressive treatments. However, in its early stages sepsis often presents itself in a nonspecific manner making it difficult to recognize and diagnose. Typical clinical characteristics of sepsis are not always obvious, sepsis is often underrecognized and its mortality remains high (Silva, Andriolo, Atallah, & Salomão, 2013).

Sepsis is predominantly detrimental among vulnerable and susceptible populaces such as the immunocompromised, young children, and older adults. Older age is an independent predictor of sepsis mortality (Martin, Mannino, & Moss, 2006). Persons older than 65 years of age with multiple comorbidities are at a higher risk for complications from infections than the general population. Presentation of early sepsis is particularly ambiguous in this age group; therefore, a lower threshold and a higher index of suspicion are required to identify sepsis in older patients (Nasa, Juneja, & Singh, 2012).

Similarly, recognizing sepsis can be delayed in patients with an impaired immune system such as those with diabetes, HIV/AIDS, hepatic failure, alcohol dependence, or who had organ transplants. Other high-risk populations are those patients with altered physiology such as pregnant or postpartum women. Neonates and young infants are at particularly high risk because they have immature immune systems.

While sepsis affects people of all ages, races, and genders, it is especially damaging and more frequently fatal among underprivileged and disadvantaged populations (Martinet al., 2006). Variations in age, gender, and medical comorbidities including diabetes and renal failure create additional complexity that influences the outcomes in septic patients (Iskander, Osuchowski, Stearns-Kurosawa, Kurosawa, Stepien, Valentine, & Remick, 2013).

Currently, there is no specific single pharmacological intervention or therapeutic measure for sepsis, with the exception of antibiotics; therefore, the care of septic patients remains mainly supportive, and even with optimal currently available therapy, septic patients still experience unacceptably high morbidity and mortality (Iskander, et al., 2013). Saving lives depends not just on treatments specific to a particular infection, but rather a focus on early recognition and awareness of sepsis, rapid antimicrobial therapy and resuscitation, and vital organ support (World Sepsis Day, 2015).

Scope of the Problem

Sepsis is a medical emergency where each hour matters. Chances of survival can be greatly improved by rapidly recognizing the condition and responding with appropriate approaches such as appropriate antimicrobial therapy (AAT) and prompt resuscitation. For many years, the inflammatory dynamics of sepsis have been incompletely understood. Over two decades ago, sepsis was first recognized as an inflammatory response to infection, and our understanding of the mechanism of the septic process and pathophysiology has evolved over time. Years of research and multiple clinical trials have been conducted; however, optimal treatments and best practice strategies are still controversial today, partially because the pathophysiology of sepsis is

still not entirely understood. Despite best available treatment, sepsis continues to be a major cause of morbidity and death (Iskander, et al., 2013).

Although implementation of early, rapid, aggressive treatment has improved mortality, those who survive sepsis frequently suffer from severe long-term consequences of later onset morbidity, permanent disability, and premature death. Septic patients often develop recurrent infections, nutritional deficiency, and sustainable organ injury before leaving the hospital in a debilitated functional state and often are rehospitalized with returning infection (Iskander, et al., 2013). Many are left with sustainable physical and mental impairments; some are on permanent hemodialysis or have amputated limbs. While some studies have shown a positive effect of early aggressive treatment, others have found no benefit compared with usual care. Optimal sepsis management strategies still need to be determined, and more research is needed to address the best practice. Our understanding of the mechanisms and complexity of sepsis pathophysiology presents substantial challenges to finding innovative treatments. Despite extensive research, currently available therapies do not provide a cure. A more individualized approach to developing improved therapeutic response is needed (Iskander, et al., 2013).

It is expected that the incidence of sepsis will continue to grow in a milieu of antimicrobial resistance, aging populations, wider use of immunosuppressive therapies, and more accessible medical technology and interventions. Despite an overall decline in the proportional mortality from sepsis, the total number of patients dying from sepsis is greater than in the past; moreover, sepsis survivors have increased long-term mortality, and are often left with considerable functional deficits and decreased the quality of life (Martin, Mannino, Eaton, & Moss, 2003).

Mortality

Sepsis is a serious global healthcare problem. More common than heart attack and claiming more lives than any cancer, sepsis remain major global health problems with an estimated number of deaths between 15-19 million per year worldwide (Tiru, et al., 2015). Although sepsis accounted for approximately 2% of all hospitalizations in 2008 in the United States, it was responsible for 17% of hospital deaths, and patients hospitalized with sepsis were sicker, and stayed longer (Hall, Williams, & DeFrances, 2014). Sepsis is currently the 10th leading cause of death in the United States and the 10th leading cause of death in South Carolina (Centers for Disease Control and Prevention, 2014).

In developed countries, sepsis is a leading cause of mortality. In the United States alone, there are 750,000 cases and 200,000 deaths from severe sepsis annually (Wang et al., 2010). Each year in the United States, sepsis results in 570,000 emergency department visits, and has a 20% to 50% mortality rate (Perelman School of Medicine at the University of Pennsylvania, 2013). In 2011, nearly 40% of sepsis cases resulted in death within 28 days (Stearns-Kurosawa, Osuchowski, Valentine, Kurosawa, & Remick, 2011). In 2014, the overall mortality rate increased to above 50%, with even higher mortality rates in patients with ischemic bowel, central nervous system (CNS) infection, disseminated infection, and other intra-abdominal infection. Somewhat lower mortality rates occur in those with obstructive uropathy-associated urinary tract infection, enterocolitis/diverticulitis, pyelonephritis, cholecystitis/cholangitis, and intravascular catheter infection (Leligdowicz et al., 2014).

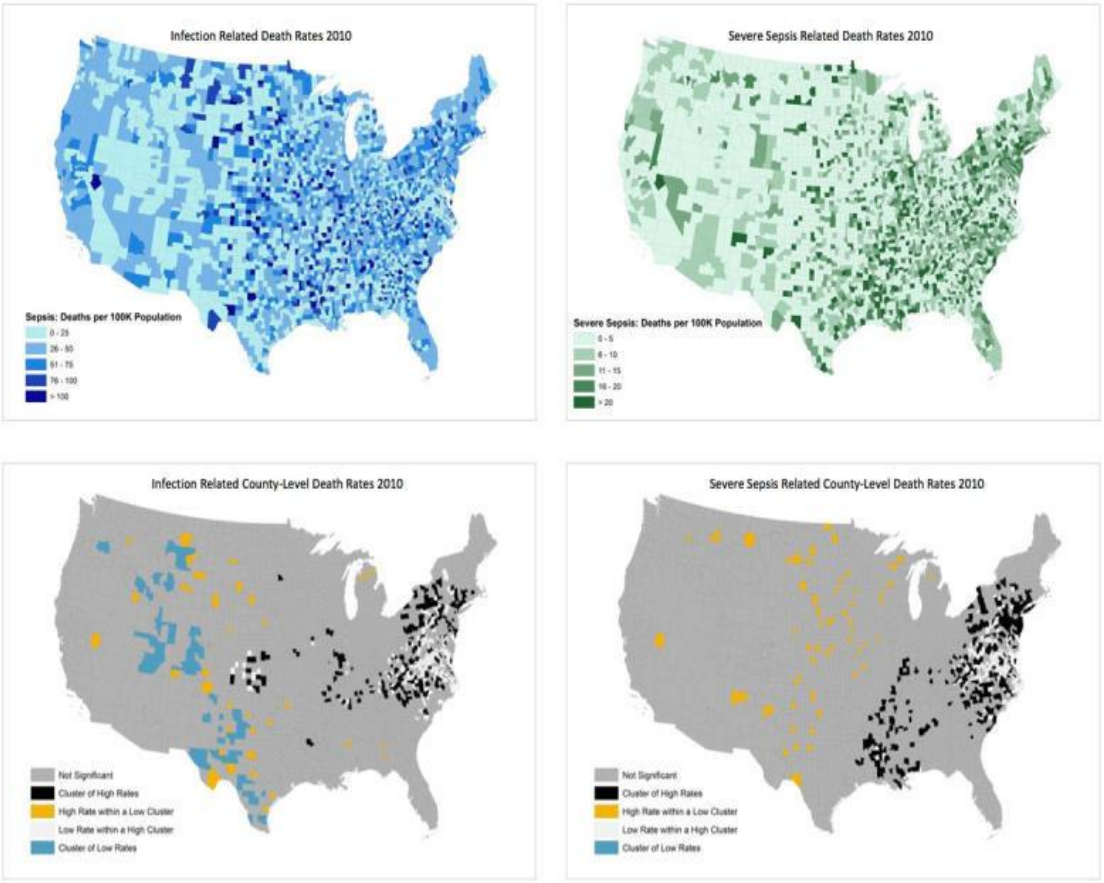

Figure I.1. Sepsis Hotspots in the U.S.
Credit: Penn Medicine (Perelman School of Medicine at the University of Pennsylvania, 2013)

Regional Distribution

The regional distribution of sepsis provides important insights. Researchers have created the first United States map that pinpoints hotspots for infection and severe sepsis related-deaths (Figure I.1). Areas with the highest sepsis mortality form contiguous clusters in the Southeastern and mid-Atlantic regions. Researchers have sought to determine the geographic distribution of sepsis to determine which areas of the country require vital public health resources and identified "hotspots" with notable clusters located in the Midwest, mid-Atlantic, and the South (Perelman School of Medicine at the University of Pennsylvania, 2013).

Sepsis in South Carolina. South Carolina has one of the highest sepsis attributed death rates, ranking 37th in the nation, carrying an inpatient hospitalization mortality rate of 14%. The annual sepsis incidence rate is 74.4 per 100,000 residents, as compared to Minnesota's 41.0 per 100,000 inhabitants (Wang, Devereaux, Yealy, Safford, & Howard, 2010). In South Carolina, sepsis is one of five top all-payer admission drivers; for Medicare beneficiaries, it is the number one driver of 30-day readmissions (21.3%). Higher rates of sepsis have been reported among South Carolina's minorities, underprivileged, and the elderly. According to United States Census Bureau (2014), 5% of the Beaufort County population that is 65 years and older lives below poverty level. Per DHEC's publicly available data on Hospital Compare website for Beaufort County, hospitals show the same or lower than the state average rate of the diagnosis of sepsis (DHEC 2015).

Risk factors

Risk factors for sepsis and death from septic shock include chronic debilitating conditions such as diabetes, treatment with immunosuppressant drugs, use of invasive procedures and devices, the presence of lines, catheters, intravascular or prosthetic devices, and genetic factors (Dellinger et al., 2013). Factors associated with increased risk of developing sepsis also include complicated obstetric delivery, certain surgeries, and trauma to the gastrointestinal tract, such as perforation of the small intestine, infections such as urinary tract infection, pneumonia, cellulitis, meningitis, and many others (Dellinger, et al., 2013). Additional risk factors for progression to septic shock include prolonged time between onset of manifestations and initiation of treatment for sepsis, misdiagnosis of infection, and use of ineffective antibiotics. Extended

hospitalization is associated with additional health complications, nosocomial infections, and increased costs. Elderly patients are more prone to prolonged length of hospital stay (LOS).

Survivors of sepsis are at increased risk of recurrent infections during the year following their septic episode. They are 2.83 times more likely to develop a subsequent infection, 3.78 times more likely to require rehospitalization for infection, and 3.61 times more likely to die after hospital discharge (Wang et al., 2014). Sepsis has been associated with the development of at least one new physical limitation for survivors and a 3-fold risk of developing moderate to severe cognitive impairment (Iwashyna, Ely, Smith, & Langa, 2010). Sepsis survivors report deterioration in the quality of life related to poor physical function and overall declined health (Turi & Ah, 2013).

Epidemiology

Incidence. Sepsis can be acquired both in the community and in healthcare facilities. CDC's National Center for Health Statistics (NCHS, 2011) estimated hospitalization with sepsis increased from 621,000 in the year 2000 to 1,141,000 in 2008. Every minute one patient presents to emergency rooms with severe sepsis (Palleschi, Sirianni, O'Connor, Dunn & Hasenau, 2014). It is projected that by the year 2020 an additional 1,000,000 sepsis cases per year will occur in the United States due to the aging population, the longevity of persons with chronic diseases, the spread of antibiotic-resistant organisms, an increase in invasive procedures, and increased use of immunosuppressive and chemotherapeutic agents (Palleschi, Sirianni, O'Connor, Dunn & Hasenau, 2014). Although epidemiologic data from 2004 to 2009 demonstrated a decrease in in-hospital mortality from 35% to 26%, severe sepsis is the third most

common cause of death in the United States, after heart disease and malignant neoplasms (Marik, 2014). Moreover, the incidence of sepsis increases an average of 13% every year (Tiru et al., 2015). As a comparison to the rest of the world, this trend is also seen in Australia, New Zealand, and in Europe. Population-based studies in the developed world showed considerably increasing the burden on healthcare systems as populations in these countries aged (Tiru et al., 2015).

Severe sepsis occurs disproportionally in hospitalized patients, 0.2:1,000 in children and 26.2:1,000 in adults who are older than 85 years of age (Schub & Schub, 2015). The incidence of severe sepsis and septic shock is growing in the United States due to the growing number of older adults, as well as high-risk patients in the general population such as those immunocompromised with diabetes, on chemotherapy, or with organ transplants. Moreover, increased sepsis occurrence is associated with greater use of invasive procedures in healthcare settings, the use of broad-spectrum empiric antimicrobials, and inappropriate prescribing of antibiotic, which promotes breeding of resistant organisms.

Pathogenesis

The pathogenetic mechanisms associated with sepsis are remarkably complex. In humans, pathogens are normally eradicated by immune and physiologic responses restricted to a local infection site and the system returns to homeostasis. Normally the immune system reacts to a source of infection by localized inflammation, where blood vessels swell to allow more blood to flow, and become leaky so that the infection-fighting cells and clotting factors can get out of the blood vessels and into the tissues where they're needed (World Sepsis Day, 2015).

Sepsis is characterized by inappropriate regulation of these normal reactions and rapid acceleration of the pathologic processes. The normal immune reaction goes to overdrive affecting all of the body organs and tissues, leading to widespread inflammation, poor perfusion, organ failure and septic shock (World Sepsis Day, 2015).

A number of biological mechanisms are activated leading to a cascade of events on molecular and cellular levels, such as upregulation of lymphocyte costimulatory molecules and rapid lymphocyte apoptosis, delayed apoptosis of neutrophils, enhanced necrosis of cells and tissues, consequently dysfunctional coagulation mechanisms, namely inappropriate intravascular fibrin deposition and disseminated intravascular coagulation (DIC) (Stearns-Kurosawa, Osuchowski, Valentine, Kurosawa, & Remick, 2011). The paradox of DIC in the late stage of sepsis is that the patients are undergoing nearly unrestricted clotting and, as a result, are at high risk for bleeding because platelets and coagulation factors are consumed faster than they can be replaced, resulting in prolonged clotting times. In septic shock organ damage may occur because small clots form faster than they can be broken down, and they lodge in the microvascular beds of organs, causing ischemia (Stearns-Kurosawa et al., 2011).

Pathophysiology. Sepsis is a potentially fatal host response to infection that occurs in association with systemic inflammatory response syndrome (SIRS). SIRS is a severe inflammatory reaction that is diagnosed when two or more specific criteria are present, such as high or low temperature, increased heart rate, and respiratory rate, decreased oxygenation, leukocytosis or leukopenia, and the presence of immature neutrophils in the bloodstream (Table II.1) (Schub & Schub, 2015). SIRS can occur with

or without an infection, but sepsis can only be diagnosed when SIRS occurs in a person with a suspected or confirmed infection (Schub & Schub, 2015).

The sepsis response is a characteristic cascade of mechanisms leading to massive vasodilation and results in a drop in blood pressure, which in turn inhibits adequate tissue perfusion that can be associated with a multiple-organ failure. Severe sepsis is characterized by multiple-organ dysfunction that results in septic shock, which is a severe sepsis with persistent hypotension despite adequate fluid resuscitation, consequently leading to death (Schub & Schub, 2015). The pathophysiological basis of sepsis has been subject to constant change over the last decades. In today's understanding, sepsis is primarily pathology of the immune system, triggered by an underlying infection but perpetuated by the host's response itself (Uhle, Lichtenstern, Brenner, & Weigand, 2015).

Sepsis Etiology

The mechanisms of sepsis are not fully understood, making treatment difficult. Infection is the most common cause of sepsis; however, in many sepsis patients, the etiology is not clearly identified. Bacteria are by far the most common culprits, but most types of microbes can cause sepsis, including bacteria, fungi, viruses and parasites such as those causing malaria (World Sepsis Day, 2015). The bloodstream, skin, respiratory, gastrointestinal, and genitourinary tracts are common sites of infection associated with sepsis. Most infections are bacterial in origin but can also be fungal, viral, rickettsial, or parasitic (Schub & Schub, 2015). The most common pathogens that cause sepsis are associated with a high risk of hospital mortality are gram-positive bacteria including staphylococci, enterococci, and streptococci, and from gram-negative spectrum including

Escherichia coli, *Pseudomonas*, *Klebsiella*, *Proteus*, and *Pseudomonas.* A list of common pathogens is shown in Appendix C Table C.1.

Presentation

Sepsis occurs as a result of infections such as pneumonia, urinary tract infections, skin and wound infections, or from invasive medical procedures. Sepsis presentation might include fever or hypothermia, hyperventilation, tachycardia, shaking chills, warm skin, skin rashes, lethargy, confusion, coma, hyperglycemia, muscle weakness, bleeding diathesis, increased cardiac output, and signs and symptoms that reflect the primary site of infection (e.g., diarrhea, abdominal pain, and abdominal distention in cases of gastrointestinal infection; severe headache, neck stiffness, and cervical/submandibular lymphadenopathy in cases of head and neck infection). Severe sepsis and septic shock are demonstrated by single or multiple organ failures such as a liver dysfunction (e.g., jaundice), cool skin, pancreatitis, renal failure, decreased cardiac output, acute respiratory distress syndrome, multiple organ dysfunction syndrome, encephalopathy, neuropathy, and DIC (Kalil, 2015).

Sepsis and Health Disparities

Biology, Geography, Climate, Environment

The type of organism causing severe sepsis is an important determinant of outcome. Gram-positive organisms as a cause of sepsis have increased in frequency over time and are now almost as common as gram-negative infections, likely due to greater use of invasive procedures and the increasing proportion of hospital-acquired infections. More frequent use of broad-spectrum antibiotics in increasingly sick patients hospitalized

for longer periods of time resulted in an increased bacterial resistance to antibiotics (Mayr, Yende & Angus, 2014).

Severe sepsis is more common in colder months. The fatality rate for sepsis is also higher in winter, despite similar severity of illness. Sepsis related to respiratory infections has the highest incidence in colder months, whereas genitourinary infections are more frequent in summer. This seasonal variation relates to climate and is reflected by the regional differences within the US: incidence variation is highest in the Northeast and lowest in the South (Mayr et al., 2014).

Disparities among gender, race, age and socioeconomic status. Low socioeconomic status, older age, male gender, African American race, and increased burden of chronic health conditions are important risk factors for severe sepsis. Psychosocial stressors, such as coping styles, housing and neighborhood quality, consumption potential (e.g. the financial means to buy healthy food, warm clothing, etc.), and the physical work environment shape health outcomes (WHO, 2010).

Epidemiological studies consistently report a higher incidence of severe sepsis among Black compared to White patients. The underlying mechanisms of racial disparities in infection and severe sepsis are poorly understood. A higher prevalence of chronic kidney disease and diabetes, higher infection rates, overall lower socioeconomic status and education levels among Black patients may partly explain higher sepsis rates (Mayr, Yende & Angus, 2014).

Women appear to be at lower risk of developing sepsis than men. Men and alcoholics are particularly prone to developing pneumonia while genitourinary infections are more common among women (Mayr, Yende & Angus, 2014). Other determinants

that shape health outcomes are behavioral factors such as nutrition, physical activity, and tobacco and alcohol consumption. Mayr et al., (2014) reported an inverse relationship between socioeconomic status and the risk of blood stream infection. A combination of race, age, comorbidities and social and environmental factors all contribute to severe sepsis-related hospitalization rates and poor outcomes. Other risk factors include residence in long-term care facilities and institutions, malnutrition, immunocompromised state and utilization of prosthetic devices (Mayr et al., 2014).

Disparities in sepsis incidence and mortality rates are higher for those underprivileged who live in medically underserved areas (DHHS, 2014). Racial disparities are associated with residence in medically and economically underserved areas, median income, percent below the poverty level and educational attainment. African Americans in South Carolina have a higher overall incidence rate of hospitalization for sepsis than Caucasians (6.09 vs. 4.74 per 1,000; $p<0.0001$) (Rice, Nadig, Simpson, Ford, & Goodwin, 2014). Large disparities exist in the incidence of sepsis in African Americans, males, and in older adults in South Carolina (Esper, Moss, Lewis, Nisbet, Mannino, & Martin, 2006).

The risk of dying from severe sepsis is considerably higher in elderly people, with age as an independent risk factor for mortality (Nasa et al., 2012). Additional risk factors for the elderly population include the presence of multiple comorbidities, inadequate financial and healthcare resources, poor nutritional status, and lack of social support. Infections in older adults often have ominous signs and are underrecognized in this high-risk population (Umberger, Callen, & Brown, 2015). Clinical presentation is often

atypical, posing challenges in regards to sepsis recognition and leading to a delayed diagnosis (Girard, Opal, & Ely, 2005).

Sepsis in the elderly population. Sepsis in the elderly population is a common problem associated with considerable mortality and major consumption of healthcare resources, and its incidence increases with age. Sepsis carries an unfavorable prognosis for all age groups, but the elderly are among the most vulnerable and particularly predisposed to sepsis (Martin et al., 2006). This is attributable to many risk factors such as the age itself, multiple comorbidities, and the fact that older patients tend to be treated less aggressively (Destarac & Ely, 2001). Clinicians must be keenly aware of nonspecific expression of sepsis in this patient population, which include delirium, weakness, anorexia, malaise, urinary incontinence, or falls (Girard, Opal, & Ely, 2005). Fever may be blunted or absent, tachycardia and hypoxemia incidences can be lower among patients with sepsis who were >75 years of age, and compared with younger patients, tachypnea and altered mental status were more common among older patients (Girard et al., 2005). Many elderly patients respond well to the evidence-based diagnostic and management strategies if initiated in a timely manner. Delayed recognition can lead to treatment failures (Girard et al., 2005).

An estimated 60-65% of all patients who develop sepsis in the United States are 65 years of age or older (Girard et al., 2005). The population of those aged 65 and older in the United States increased 13.2% from 1990 to 2000 and continues to grow. In 2050, the number of adults aged 65 and older is projected to double from 2012 and reach 83.7 million (AHR, 2014).

The aging of the population in developed countries is believed to be largely responsible for the increased incidence of sepsis (Martin et al., 2006). Those aged 65 and over tend to be hospitalized for sepsis longer than the average length of stay (LOS), and had an average LOS that was 43% higher than that of other patients. In those aged 65 and over, 20% of sepsis hospitalizations ended in death compared with 3% for other reasons for hospitalizations in general (Hall, Williams, & DeFrances, 2014).

Financial Implications

Sepsis is the costliest diagnostic condition. Sepsis ranks number one for all-payer hospital discharges, exceeding one million discharges a year and representing 5.2% of all healthcare costs, and consuming 6.9% of Medicare payments annually. Sepsis contributes to $20.3 billion in aggregate hospital costs to the annual economic burden of the national healthcare system (Torio & Andrews, 2013). A major factor driving these expenditures is that the average length of hospitalization for sepsis patients is 75 percent longer than stays for other conditions (Hall, Williams, & DeFrances, 2014). However, long-term consequences of sepsis draw attention to the true magnitude of this problem. The total cost of sepsis treatment and care in the United States has been estimated at $400 billion annually (Lopez-Bushnell, Demaray, & Jaco, 2014). The cost of treating a patient in the ICU with severe sepsis is 6 times greater than the cost of treating a patient in the ICU who does not have sepsis (Ahrens & Tuggle, 2004).

As the impact of survivorship increases, the cost to society extends well beyond lives lost (Tiru et al., 2015). Increased dependence and rehospitalizations of sepsis survivors increase healthcare consumption and, along with increased mortality, all contribute to the humanistic burden of severe sepsis (Tiru et al., 2015). While

socioeconomic positions shape specific determinants of health status, sepsis accounts for disproportionate resource utilization and substantial mortality.

Description of the Clinical Problem

Sepsis is a major public health problem. Early identification and treatment save lives and resources. It is a life-threatening condition that can rapidly progress to severe sepsis, septic shock, multi-organ failure, and death. It is a serious, costly, often lethal condition, and a common problem for most hospitals. Despite advances in technology and some improvement in survival rate over last decade, sepsis continues to have high mortality and poor outcomes.

Like the rest of the nation, a community-based, 100-bed hospital located in coastal South Carolina has been experiencing a high incidence and mortality of sepsis and struggling with poor patient outcomes. This hospital is a part of a large healthcare organization that is composed of hospitals across the United States. This facility has implemented the Surviving Sepsis Campaign (SSC) clinical guidelines as new protocols for sepsis care in efforts to improve outcomes. Prior to the launching of the Sepsis Bundle program the hospital was using previously established standards of care based on evidence-based practice, however, these were applied inconsistently per individual provider discretion. As of October 1, 2015, this hospital has implemented a set of new protocols for sepsis management, as proposed by SSC guidelines, including the updated 3- and 6-hour management bundles. It included all the newest components of SSC guidelines and preparation for implementation included staff education. An update to existing Electronic Medical Record software was also implemented to recognize and stratify patients with sepsis. The new update allowed the introduction of a new

computer-assisted sepsis alert to improve early recognition. The EMR now includes clinical decision support system that helps to detect patients at risk of sepsis based on entered values. The system alert is triggered by pre-programmed specific to sepsis vital signs and laboratory values, and once activated, generates tasks for clinical staff. The alert is delivered as a pop-up notification to the patients' designated nurse, who then electronically contacts a provider. The provider also receives an alert and is obligated to document that action was taken (Amland, Lyons, Greene, & Haley, 2015). A sepsis screening assessment task was also integrated into admission order sets in order to improve the process of determining sepsis risk and facilitate recognition early in the admission process.

Patient demographic characteristics in this hospital are diverse, but many are elderly, over the age of 65, and many visiting the area. This demographic profile accurately reflects population distribution in the county (Table I.1) (United States Census Bureau, 2014).

Table I.1. *South Carolina and Beaufort County Population >65 Demographic*

	Selected County	**SC State**
	count	count
Population, 2014 estimate	175,852	4,832,482
	%	%
Persons 65 years and over, % 2013	23.3	15.2

(United States Census Bureau 2014).

Project Background

Given the specific population characteristic for this hospital, with an average age of patients with sepsis being 74 years, the original intent of this project was to retrospectively evaluate elderly patients who were admitted to the hospital with sepsis or

who developed sepsis while hospitalized. Diagnosing sepsis in this population is more difficult because elderly patients may have an atypical response and a subtle, ambiguous presentation of sepsis, such as altered mental status or falls. Therefore, lifesaving treatments and therapeutic interventions for this population may often be delayed (Destarac & Ely, 2001). Altered mental status in elderly patients may sometimes be the sole symptom of sepsis on initial presentation; as a result, there is a high possibility that a number of these patients are underdiagnosed. Given the atypical presentation of sepsis in elderly patients, potential underdiagnosis likely contributed to negative outcomes in my practice setting.

The initial purpose of this project was to illustrate an innovative approach to initial sepsis screening in the emergency room and inpatient care that could facilitate earlier recognition of sepsis among the elderly, and potentially improve sepsis survival in this patient population. This would have been accomplished by adding a short cognitive assessment to evaluate for acute mental status change, and including it as one of the SIRS manifestations and a diagnostic criterion for severe sepsis.

While the core clinical staff and leaders were initially supportive, and the majority of staff agreed that it would be a good step towards improving sepsis recognition among the elderly, the idea met solid resistance for any attempt for implementation. Upon further assessment, it became clear that the nursing and clinical staff in both the emergency department and on units already felt overwhelmed with the number of assessments required of them, and the notion of one more, even a brief one, was not welcomed. Additionally, integration of a new assessment into the existing module in the electronic medical record software could possibly be a difficult and costly process.

Given this development, the project was re-routed to focus on current sepsis guidelines effectiveness and evaluation of their impact on patients' health outcomes after the protocol implementation. I am a member of an interdisciplinary team dedicated to improving sepsis outcomes in this setting, and we are considering potential improvements in diagnostic technology that would allow earlier identification of pathogens and targeted treatment.

Evaluation of the success of changes that have already been implemented will provide valuable data to guide the direction of future practice innovation. For innovations that require organizational financial outlays, it is necessary to demonstrate the need for such an investment as well as the potential benefit relative to cost. Therefore, the first step is to assess the impact of recently implemented protocols.

Purpose of the Project

The purpose of this project was to evaluate the utilization and effectiveness of current sepsis protocols in a community hospital in coastal South Carolina on health outcomes. Specifically, to assess whether the protocol affected hospital length of stay, mortality, morbidity, readmissions, appropriateness of antibiotics utilization, and influenced the timing of initiating of interventions. Facilitators and barriers were identified and examined. Findings are to be integrated with collaborative sepsis team efforts, and the best practice recommendations will be presented to the hospital administration. The ultimate goal of the project was to facilitate innovative approaches to diagnostic methods and inpatient care that could improve sepsis treatment approach and outcomes.

PICO Question

The PICO question was formulated using the format developed by Melnyk and Fineout-Overholt (2011) to identify the specific target population, the intervention of interest, comparison of intervention, outcomes and the time frame.

- [P] *Population*- Population of Selected Subjects
- [I] *Intervention*- Experimental Intervention
- [C] *Comparison* - Comparison of Intervention
- [O] *Outcomes*- Results and Outcomes of Interventions
- [T] *Time* -Time Frame

(Melnyk &. Fineout-Overholt, 2011, para. 4).

The PICO question used to guide this project was: In adult patients presenting with sepsis before and after October 1, 2015, does implementation of a new sepsis protocol reflect in improved outcomes such as reduced hospital LOS, decreased mortality, morbidity, readmissions, and appropriate antibiotics utilization, and does it result in initiating early treatments as compared to previous approaches?

The focus of the question was to evaluate the effectiveness of early interventions, further identify the components of the current sepsis "bundles" protocol that are most effective in the treatment and the most accurate in early recognition of sepsis, and explore the degree to which the components favor clinical staff compliance and contribute to improved patient outcomes.

Definitions

Appropriate Antibiotic Therapy (AAT) in patients with severe sepsis and septic shock means prompt achievement of antimicrobial's therapeutic concentration in blood, tissue penetration, and maintenance of optimal exposure at the infection site with broad-spectrum antibiotics administered in a timely manner – as per the guideline protocol (Pea, & Viale, 2009).

Bacteremia: Invasion of the bloodstream by bacteria (Gale Encyclopedia of Medicine, 2008).

Blood cultures: Incubation of a sample of blood in a suitable culture medium so as to encourage reproduction of bacteria, which are possible causes of disease, for purposes of identification (Collins Dictionary of Medicine, 2004).

Bundle: A group of interventions related to a disease process that, when executed together, result in better outcomes than when implemented individually (Dellinger &Vincent, 2005, p. 635).

Coagulation: Clotting; the process of changing from a liquid to a solid, said especially of blood (that is, blood coagulation). In vertebrates, blood coagulation is a result of cascade regulation from fibrin (Farlex Partner Medical Dictionary, 2012).

Comorbidity: Coexisting medical conditions or disease processes that are additional to an initial diagnosis (Mosby's Medical Dictionary, 2009).

Crystalloid: A hydration solution that contains only electrolytes; a substance in a solution that can diffuse through a semipermeable membrane (Mosby's Medical Dictionary, 2009).

Extravascular: Outside the blood vessels or lymphatics or of any special blood vessel (Farlex Partner Medical Dictionary 2012).

Fibrin: An insoluble protein that is essential for clotting of blood, formed from fibrinogen by the action of thrombin (Dorland's Medical Dictionary, 2007).

Hyperventilation: Unusually or abnormally deep or rapid breathing; hyperventilation is defined as breathing in excess of the metabolic needs of the body, eliminating more carbon dioxide than is produced, and, consequently, resulting in respiratory alkalosis and an elevated blood pH. The traditional definition of hyperventilation syndrome describes "a syndrome, characterized by a variety of somatic symptoms induced by physiologically inappropriate hyperventilation and usually reproduced by voluntary hyperventilation" (Folgering, 1999, p. 365).

Hypoperfusion: A condition of acute peripheral circulatory failure due to derangement of circulatory control or loss of circulating fluid. It is marked by hypotension and coldness of the skin, and often by tachycardia and anxiety (Miller-Keane Encyclopedia, 2003):

Hypotension: Diminished tension; lowered blood pressure, systolic pressure less than 100 millimeters of mercury (mmHg) (Miller-Keane Encyclopedia, 2003).

ICU: Intensive Care Unit.

Immunocompromised: Also immunosuppressed, having impaired immune system, prone to infection and more severe infection course.

Initial sepsis presentation: "Time zero" or sepsis onset, or onset of manifestations. While pinpointing exactly the time of sepsis onset is difficult, if not impossible, it is the time of reference that specific symptoms characteristic to sepsis were observed and documented, also a marker for quality measures.

In vitro: Within a glass; observable in a test tube; in an artificial environment (Miller-Keane Encyclopedia, 2003).

Lactic acid: A compound formed in the body in anaerobic metabolism of carbohydrate and also produced by bacterial action (Dorland's Medical Dictionary, 2007).

Length of Stay (LOS): It is the length of an inpatient episode of care, the number of days patient stays in a hospital, calculated from the day of admission to day of discharge, and based on the number of midnights spent in the hospital. Patients admitted and discharged on the same day have a length of stay of less than one day (McGraw-Hill Concise Dictionary of Modern Medicine, 2002)

Leukocytosis: An increase in the number of white cells in the blood, especially during an infection. The presence of more than 11,000 white cells in a cubic millimeter of blood is considered high.

Morbidity: A diseased condition or state.

Morbidity rate: The number of cases of a particular disease occurring in a single year per a specified population unit, as x cases per 1000. It also may be calculated on the basis of age groups, sex, occupation, or another population unit (Mosby's Medical Dictionary, 2009).

Mortality: The death rate, which reflects the number of deaths per unit of population in any specific region, age group, disease, or other classification, usually expressed as deaths per 1000, 10,000, or 100,000 (Mosby's Medical Dictionary, 2009).

Multi-drug resistance: The resistance of bacteria, especially against more than two of the antibiotics that were once effective (Mosby's Medical Dictionary, 2009).

Oliguria: Scant urine production, diminished capacity to form and pass urine, less than 500 mL in 24 hours.

Organ hypoperfusion: It may be demonstrated by an increase in serum lactate level, oliguria, an acute alteration in mentation, or altered circulation to the peripheral extremities. Organ dysfunction is often evidenced by arterial hypoxemia, acute respiratory distress syndrome (ARDS), acute renal failure, thrombocytopenia, and/or disseminated intravascular coagulation (DIC).

Pathogen: Any disease-producing agent or microorganism (*Miller-Keane* Encyclopedia, 2003):

Pathophysiology: The study of structural and functional changes in tissue and organs that lead to disease, also derangement of function seen in disease; alteration in function as distinguished from structural defects (Farlex Partner Medical Dictionary, 2012).

Perfusion: The act of pouring through or over; especially the passage of a fluid through the vessels of a specific organ (Miller-Keane Encyclopedia, 2003).

Permeability: A condition of the capillary wall structure that allows blood elements and waste products to pass through the capillary wall to tissue spaces *(*Mosby's Medical Dictionary, 2009).

Polymerase chain reaction (PCR): A rapid technique for in vitro amplification of specific DNA or RNA sequences, allowing small quantities of short sequences to be analyzed without cloning (Miller-Keane Encyclopedia, 2003).

Readmission or *rehospitalization*: Defined as an admission to a hospital within 30 days of a discharge (CMS, 2014). The return of a patient to inpatient hospital care shortly after discharge (typically within 30 days of discharge) (Farlex Medical Dictionary, 2009).

Sepsis: Referred to as bloodstream infection or blood poisoning, infections are the cause of sepsis and can originate anywhere from within the body. It is the presence of various pathogenic organisms, or their toxins, in the blood or tissues (Farlex Partner Medical Dictionary, 2012). Some of the more common sites include liver or gallbladder, kidneys, lungs, bowel, and skin (Medline Plus, 2006).

Severe Sepsis: It is the presence of defined sepsis in addition to organ damage, hypoperfusion, organ dysfunction, or hypotension. A condition defined clinically as 'Sepsis associated with organ dysfunction, hypotension, or hypoperfusion abnormalities such as lactic acidosis, oliguria, or an acute alteration in mental status; it is part of a continuum of a biologic inflammatory response to infection that evolves toward septic shock *(*McGraw-Hill Concise Dictionary of Modern Medicine, 2002).

Septic shock: A possible consequence of bacteremia; bacterial toxins, and the immune system response to them, cause a dramatic drop in blood pressure, preventing the delivery of blood to the organs, despite resuscitative attempts. Septic shock can lead to multiple-organ failure including respiratory failure, and may cause rapid death (Gale Encyclopedia of Medicine, 2008).

Tachycardia: An abnormally rapid heart rate, especially one above 100 beats per minute in an adult (American Heritage Dictionary, 2011).

Vasodilation: Widening of the lumen of blood vessels (Farlex Partner Medical Dictionary 2012).

Vasopressor: A drug producing vasoconstriction and a rise in systemic arterial blood pressure (Farlex Partner Medical Dictionary, 2012).

Supporting Framework

Model for improvement

A model for improvement was utilized as the framework and guide for this quality improvement project. The model is based on W. Edwards Deming's Plan-Do-Study-Act (PDSA), which has been widely used in healthcare improvement programs (Langley et al., 2009). PDSA cycles provide a structure for iterative testing of changes to improve the quality of systems. This method tests a change before its implementation by planning it, trying it, observing the results and acting on what is learned with the overall objective of improving the process or outcome (Van Tiel et al., 2006). The PDSA cycle presents a pragmatic scientific method for testing changes in complex systems (Moen & Norman, 2006) and in a small scale. These pragmatic principles of PDSA cycles endorse measurements over time to assess the impact of interventions, promote prediction of the outcome, and allow the use of small-scale, iterative approaches to test interventions, which enables rapid assessment and provides flexibility to adapt the change (Taylor et al., 2014).

The four stages - plan, do, study, and act - mirror the scientific experimental method of formulating a hypothesis, collecting data to test this hypothesis, analyzing and interpreting the results and making inferences to iterate the hypothesis (Speroff & O'Connor, 2004). There are two similar approaches to process improvement: a Plan-Do-Study-Act (PDSA) (Langley et al., 2009) and Plan-Do-Check-Act (PDCA) (Bushell, 1992). The PDSA cycle was originally developed by Walter A. Shewhart as the PDCA cycle. W. Edwards Deming modified Shewhart's cycle to PDSA, replacing "Check" with "Study." The terms PDSA and PDCA are often used interchangeably in reference to the

method (Taylor et al., 2014). For the purpose of this project, both PDSA and PDCA are considered but I refer to the methodologies generally as 'PDSA' cycles unless otherwise stated. Both methods are broadly accepted in healthcare process improvement activities (Taylor et al., 2014).

The process' cycles provide a structure for repetitive testing of changes to improve the quality of systems, and require that plans be tested on a small scale before implementing them system-wide. The method also builds continuous improvement into planning through data collection on the effectiveness of the new process or change (Bushell, 1992). The PDSA method to improve quality in healthcare is a change model that aims to generate advance in processes and outcomes.

The PDSA model includes two components, which comprise three improvement questions, and the PDSA cycle (Langley et al., 2009). Figure I.2 provides a visual representation of the model for improvement. The objectives of the improvement questions are to establish groundwork to guide improvement efforts, subsequently to set measurable goals, quantify measures to demonstrate improvement, and choose variables (Institute for Healthcare Improvement, 2014). The three improvement questions are:

1. What are we trying to accomplish?
    a. Set aims: identify sepsis protocols' features (individually selected components) that made a difference in the specific population.
    b. Summarize outcomes and compare findings for both pre-implementation and post-implementation groups.
    c. By using data, substantiate the need for improvement and recommend practice change.

    d. Establish and corroborate support system for this evidence-based project.

2. How will we know that a change is an improvement?
    a. Based on scientific literature establish benchmarks for review, collect data and measure outcomes. Changes should reflect in the measures.
3. What changes can we make that will result in improvement?
    a. Form a dedicated team, stakeholders buy-in and involve people in the decision-making process (Langley et al., 2009).

The second part of the model in the PDSA cycle, also called the Deming Cycle, is a four-step approach to solving problems, described as the trial-and-learn process allowing identification of the most effective solution before implementation. The method follows a prescribed four-stage cyclic learning approach to adapt changes aimed at improvement. In the 'plan' stage a change aimed at improvement is identified, the 'do' stage sees this change tested, the 'study' stage examines the success of the change and the 'act' stage identifies adaptations and next steps to inform a new cycle (Taylor et al., 2014, para. 7).

Step one: Plan

The process starts by identifying the problems (i.e., delayed recognition and treatment of sepsis) and pinpointing the root cause(s), and this was accomplished by asking a cascade of *why* questions.

1. Define objectives and identify problems such as delayed recognition and treatment of sepsis leading to high mortality and morbidity, and long waiting

time for culture results, consequently inappropriate antibiotic utilization that promotes breeding of MDR organisms.

2. Ask the PICO question and plan to answer the question.
3. Plan data collection to answer the question.
4. Recognize barriers, enabling factors, and potentially modifiable factors for sepsis management in hospitalized adults, while attempting to pinpoint the root cause.
5. Develop a pragmatic strategy to overcome barriers. Determine which issues are most significant and modifiable, which can be influenced by interventions, and which factors to manipulate in order to create changes.

Step two: Do

Potential solutions were assessed and the most practical solution determined. Many options must be taken into consideration such as stakeholders buy-in and the budget. In my practice setting, new sepsis protocols have been implemented, while additional solutions are under consideration.

1. Start to conduct study protocol by collecting baseline data and illustrating demographic characteristics.
2. Collect data for follow-up measures and data analysis.
3. Analyze data.

Step three: Study, or Check

In this phase data were analyzed, outcomes evaluated and results summarized, and any problems in the implementation of the designed intervention were identified

1. Examine and interpret results.

2. Compare patients' outcomes before and after sepsis guidelines implementation, and evaluate the impact of practice change on outcomes.
3. Evaluate compliance with each element of the new sepsis guidelines to compare the post-intervention group to prior performance to achieve a clearer picture of Sepsis Bundles impact on health outcomes.
4. Based on obtained results evaluate the need for practice change.

Step four: Act

This stage is to determine the overall success or failure of the intervention and to identify potential modifications to improve the intervention strategy. If necessary, new changes are implemented, and the cycle repeats again starting at the first step. This step is implemented in the practice setting following completion of the project.

1. Prepare and plan for the next PDSA cycle.

It is important to remember that this plan is circular. The benefits of PDSA are that it provides standardized methods to achieving continuous improvement. If used correctly it is time efficient, prevents implementing ineffective solutions and promotes teamwork. This project reflects the evaluation of outcomes following the implementation of initial practice changes, and the review of evidence may result in recommendations for further action. (See Appendix D, Figures D.1 and D.2 for PDCA cycle template and PDSA worksheet).

The cycle can be refined and repeated for Continual Process Improvement (CPI). Process evaluation is used to monitor and document program implementation and can aid in understanding the relationship between specific program elements and program

outcomes. The evaluation model is based on CDC's Framework for Program Evaluation Steps: (German et al., 2001).

1. Engage stakeholders.
2. Describe the program.
3. Focus the evaluation design.
4. Gather credible evidence.
5. Justify conclusions.
6. Ensure use and share lessons learned.

Plan-Do-Study-Act Worksheet can be used as a tool for documenting the test of change. See Appendix D, Figure D.1 and D.2 for PDSA worksheets and a template.

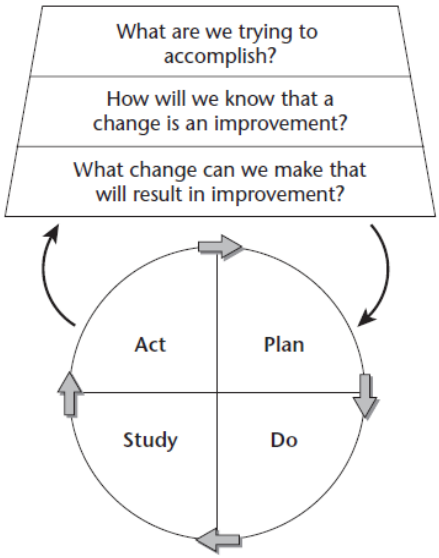

Figure I.2. Model for Improvement

(Institute for Healthcare Improvement, 2014). (Langley et al., 2009, p. 24)
Used with permission; source: The Improvement Guide: A Practical Approach to Enhancing Organizational Performance, 2nd Edition, Gerald Langley, Ronald Moen, Kevin Nolan, Thomas Nolan, Clifford Norman, Lloyd Provost. Jossey-Bass Pub., San Francisco, 2009.
See Appendix L, Figures L.1 and L.2 for permission to use images.

Summary

Despite advancing technology, availability of broad-spectrum antibiotics, improved ability to manage infections, and modern intensive care, sepsis is still associated with a substantial morbidity and mortality. Severe sepsis and septic shock represent challenging problems for the healthcare system. While aggressive supportive care with intravenous fluids and prompt antibiotics administration are critical, early recognition is paramount. Precise isolating and identification of causative pathogens will result in earlier de-escalation from broad-spectrum antimicrobials to targeted treatment with the most appropriate antibiotics. Consequently, this can result in lowering the chances of breeding multi-drug resistant organisms, reducing readmission rates, and lead to improved outcomes and reduced costs. Collaborative work of interprofessional teams and appropriate use of resources in approaches to sepsis treatment will positively affect healthcare outcomes (Vazquez-Grande & Kumar, 2015). The following chapter contains a review of the recent literature on the sepsis guidelines effects on patients' outcomes.

CHAPTER II

LITERATURE REVIEW

This chapter describes the results of a search for evidence for best practices to promote early identification and management of sepsis in the clinical setting. It outlines the search process and analysis of the evidence that was used to guide the project and subsequent recommendations.

Search Process

A comprehensive literature review was conducted in search of evidence to support recommendations for the practice innovation proposed in this paper. The process of literature review and analysis of evidence utilized the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and CINAHL Plus, Cochrane Library, PubMed, OvidSP, EbscoHost, Agency for Healthcare Research and Quality (AHRQ), National Guideline Clearinghouse databases, Google Scholar, and other evidence-based resources. Keywords and phrases used in the search for literature were: sepsis, severe sepsis, septic shock, septicemia, sepsis guidelines, inpatient sepsis, sepsis bundle, bundle treatment, SSC, and EGDT. Initial literature searches returned 27,773 articles; however, many of those were either not supportive or not pertinent to the PICO question. Therefore, limits and modifiers were applied to the search process in order to narrow results to studies that were specific to the population of interest, measured patient outcomes in contrast to

interventions, and relevant to this project. Filters included human subjects, adults, articles published in the last ten, then last five years, clinical trials, randomized controlled trials, controlled clinical trials, meta-analysis, systematic review, and peer-reviewed journal articles.

A CINAHL database search was conducted and it was limited to full-text journal articles published within last 10 years, between the year 2006 and 2016 which produced 2932 text results. Abstracts were reviewed, and in order to narrow the search and capture the most recent publications, the search was further constricted to include a new time frame from the year 2010 to 2016, with the same keywords and phrases used. Inclusion criteria were hospitalized adults who were diagnosed with sepsis. After duplicates were removed, a total of 66 potentially relevant publications were identified, of which 46 were excluded, and 26 articles that could potentially contribute to answering the PICO question were saved for further appraisal as supporting evidence. Cochrane Library database search limited to trials published within last five years included the same search terms: sepsis outcomes, treatment, guidelines, hospitalization, returned 28 full-text results. Three of those results of high scientific power were relevant to the clinical problem for this project. OvidSP database search returned 53 text results (search terms used: malnutrition and elderly and hospital), and four were found to be relevant to the clinical question. Lastly, further reapplication of the review inclusion criteria was performed and search narrowed to full-text articles, and a final list of a total of 32 potentially relevant publications meeting criteria were selected.

Review of the Literature

Overview of the Evidence

The following PICO question guided this extensive literature review and this project: In adult patients presenting with sepsis before and after October 1, 2015, does implementation of a new sepsis protocol reflect in improved outcomes such as reduced hospital LOS, decreased mortality, morbidity, readmissions, and appropriate antibiotics utilization, and does it result in initiating early treatments as compared to previous approaches?

Several studies provided evidence-based practice strategies that focused on sepsis management. Subsequently, by utilizing the criteria for evaluating studies (Melnyk & Fineout-Overholt, 2011), 21 publications that offered supporting evidence and were relevant to this project were selected. Articles were organized by type of study, and quality rating. An evidence table was developed, highlighting threats to validity and reliability, findings, and conclusions for each of the 21 articles selected (Appendix A, Table A.1). Consequently, upon completion of the selection process, articles were systematized accordingly to the level of evidence rating using the Evidence Level and Quality Guide by Johns Hopkins Nursing Evidence-Based Practice: Model and Guidelines (Dearrholt, 2012) (Appendix B, Table B.1).

The quality rating system provided an evaluation guide methodology where studies were assigned a numerical and alphabetical value based on their level of evidence. Level I was applicable for experimental studies, randomized controlled trial (RCT), and systematic review of RCTs with or without meta-analysis. Level II was appropriate for quasi-experimental studies, a systematic review of a combination of RCTs and quasi-

experimental, or quasi-experimental studies only, with or without meta-analysis. Level III applied to non-experimental study, a systematic review of a combination of RCTs, quasi-experimental and non-experimental studies, or non-experimental studies only, with or without meta-analysis, qualitative study or systematic review. Level IV applied for the opinion of respected authorities and/or nationally recognized expert committees or consensus panels based on scientific evidence. Level V was assigned to studies based on experiential and non-research evidence. Articles were also rated using quality guides and assigned a letter A for high quality, B for good quality, C for low quality or presence of major flaws.

Analysis of Evidence

Historical development of sepsis definition and guidelines

In 1991, a North American consensus conference introduced the idea that sepsis is the host's inflammatory response to infection, and SIRS was defined by four variables: temperature, heart rate, respiratory rate, and white blood cell count (Bone et al., 1992). In 2001, a second consensus conference revisited the SIRS definition, expanded the list of potential clinical criteria, but inadvertently made it less specific (Vincent et al., 2013).

As of October 1, 2015, the Center for Medicare and Medicaid Services (CMS) has issued new benchmarks for the care of severe sepsis and septic shock (Figure II. 1) that all hospitals in the U.S. must meet (Baciak, 2015). Current guidelines utilize several different definitions for sepsis, including sepsis, severe sepsis, and septic shock along with complicated strategies for systemic inflammatory response syndrome (SIRS) criteria (Table II.1 and Figure II.2). Both SIRS and severe sepsis definitions raise controversies among clinicians (Baciak, 2015). The severe sepsis definition was derived from SSC

guidelines published in 2012 and based on 2003 International Sepsis Definition Conference (Dellinger et al., 2013). SIRS and organ dysfunction definitions may be inconsistent in some cases. For example, based on the current definitions virtually all end-stage kidney or liver disease patients experiencing mild viral upper respiratory infection producing fever or leukocytosis would meet the criteria of severe sepsis and may consequently be overtreated (Baciak, 2015).

	Severe Sepsis	Septic Shock
Performed by Hour 3	1. **Initial lactate** level 2. **Broad spectrum antibiotics** administered intravenously 3. **Blood cultures prior** to antibiotics	1. **Initial lactate** level 2. **Broad spectrum antibiotics** administered intravenously 3. **Blood cultures prior** to antibiotics
Performed by Hour 6	1. **Repeat lactate if the initial lactate is elevated (>2**mmol)	1. Resuscitation with **30 cc/kg** of crystalloid fluid 2. Vasopressors if the shock is **refractory to resuscitation** 3. If hypotension is refractory to the fluids or initial lactate is ≥4 the following must be documented: a. **Repeat volume status and tissue perfusion assessment** consisting of: i. A focused physical exam performed by the provider including vital signs, cardiopulmonary exam, capillary refill evaluation, peripheral pulse evaluation, and skin exam ii. Any two of the following: 1. Central venous pressure measurement 2. Central venous oxygen saturation **3. Bedside cardiovascular ultrasound** 4. **Passive leg raise exam by provider or fluid challenge exam**

Figure II.1. Sepsis Treatment Benchmarks
(Baciak, 2015, p. 1)

Table II.1. *Criteria for SIRS*

Criterion	**Value**
Temperature	>38°C or <36°C
Heart rate	>90 beats per minute
Respiratory rate	>20 or PaCO2<32 mm Hg
White blood cell count	>12 K or <4 K mm−3, or >10% bands

For a diagnosis of SIRS to be made, two of the four criteria need to be present (Schub & Schub, 2015).

Severe Sepsis	Septic Shock
All three must be met within 6 hours: 1. Documentation of a **suspected source** of infection 2. Two or more manifestations of **SIRS** criteria: a. Temperature >38.3 C/101 F or <36 C/96.8 F b. Heart rate >90 c. Respiratory rate >20 d. WBC >12 or <4 or >10% bands 3. **Organ Dysfunction**, evidenced by any one of the following: a. SBP < 90 or MAP <65, or a SBP decrease of more than 40 pts b. Cr >2.0 or urine output < 0.5 cc/kg/hour for 2 hours c. Bilirubin >2 mg/dL (32.4 mol/L) d. Platelet count < 100 e. INR >1.5 or PTT > 60 f. Lactate >2 mmol/L 4. Or if a provider documents severe sepsis, r/o sepsis, possible sepsis, or septic shock	1. There must be documentation of septic shock present and 2. **Tissue hypoperfusion** persisting in the hour after crystalloid fluid administration, evidenced by: a. SBP < 90 b. MAP < 65 c. Decrease in SBP by >40 points from the patient's baseline d. Lactate ≥4 3. Or if the criteria are not met, but there is provider documentation of septic shock or suspected septic shock

Figure II.2. Severe Sepsis, Organ Dysfunction, and Septic Shock Definitions (Baciak, 2015, p. 1)

Systemic Inflammatory Response Syndrome

The Systemic Inflammatory Response Syndrome (SIRS) concept creates many controversies by being very nonspecific but very sensitive at the same time, meaning that a great majority of patients admitted to an ICU every day meet the SIRS criteria (Table II.1). SIRS can be caused by many non-infectious clinical processes or sterile inflammation such as severe trauma, burns, pancreatitis, and ischemic events. If SIRS is defined in the presence of infection, almost every acutely ill patient would meet the SIRS criteria; therefore, all septic patients have a known or unknown source of infection, but not all infected patients are septic (Vincent et al., 2013). Further, almost all infections, minor of major, are associated with fever - a natural body response to the presence of the pathogens. Fever is usually associated with tachycardia, leukocytosis, and even hyperventilation; nevertheless, the absence of this response may occur in the presence of microbial colonization or host's immunocompromised status, two very different clinical scenarios, not necessarily meaning sepsis (Vincent et al., 2013). Moreover, several such stressors might be present simultaneously in any patient, making sepsis difficult to diagnose. Since symptoms of sepsis can be vague especially in its early stage, all the more difficult, if not impossible, is zeroing in on the time of initial sepsis onset, such an important point of reference in current treatment guidelines and a marker for quality measures. The more accurate is a different definition of sepsis, where sepsis is not simply the host response to an infection or inflammation, but it is the "host's deleterious, non-resolving inflammatory response to infection that leads to organ dysfunction" (Vincent et al., 2013, para. 7).

Guidelines development

In 1991, sepsis was first recognized as a systemic inflammatory reaction to infection. In the following decade, a spotlight was shone on sepsis treatment and a new approach was introduced to emergency departments (ED). In 2001, a landmark article by Rivers et al. titled "Early Goal Directed Therapy (EGDT) in the Treatment of Severe Sepsis and Septic Shock" (2001) documented a noteworthy short-term and long-term mortality benefit when EGDT was implemented at the earliest stages of severe sepsis and septic shock. The concept of EGDT was treating septic patients early while still in the ED. (Rivers et al., 2001). Rivers et al. (2001) showed that utilizing EGDT resulted in marked improvement in mortality compared to standard care.

The EGDT was the first structured approach that guided the first six hours of resuscitation with more IV fluids, ionotropic support, blood transfusions; it involved insertion of central line and central venous pressure (CVP), central venous oxygen saturation ($ScVO_2$) and mean arterial pressure (MAP) measures (Yealy et al, 2015). Interventions were delivered according to specific hemodynamics, including CVP endpoint 8-12 mmHg, MAP $\geq$ 65 and $ScVO_2$ > 70% (Rivers et al., 2001). The single center randomized trial enrolled relatively a small sample of 130 treatment and 133 control patients. The study demonstrated in-hospital mortality was 30.5% in the group assigned to EGDT, compared to 46.5% in the standard therapy group in short-term treatment (p=0.009). Mortality was 33.3% in EGDT group (p=0.01) compared to and 49.2% in the control group in 28-day mortality rate, and 44.4% EGDT group (p=0.03) to 56.9% standard therapy groups in 60-day long-term mortality outcomes (Rivers et al.,

2001). Given those findings, central catheter driven approach became a mainstream treatment for sepsis at that time.

In 2002, a collaborative effort among the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, and the International Sepsis Forum resulted in the formation of the Surviving Sepsis Campaign (SSC) (Society of Critical Care Medicine, 2014). SSC is a global initiative formed to reduce sepsis-related mortality and improve short and long-term outcomes. For the past decade, SSC has been in the frontline leading the efforts to improve sepsis outcomes worldwide. Based on literature and expert opinion, SSC developed, and published, clinical practice recommendations for management of severe sepsis and septic shock, which are focused on increasing provider awareness and promoting early intervention (Haddad, Slesinger, Wie, & LoVecchio, 2015). The SSC endorsed EGDT and proposed this approach as a key strategy to decrease mortality among patients with severe sepsis or septic shock.

Since 2002, the Surviving Sepsis Campaign (SSC) has been promoting best practice guidelines that optimize oxygen delivery and tissue perfusion, thus increase patients' chances of survival. EGDT involving a six-hour resuscitation protocol became at that time the best practice strategy with objectives to maintain adequate organ perfusion, control infection, limit barotrauma due to mechanical ventilation, and control hyperglycemia (Haddad et al., 2015).

In 2010, another study demonstrated the superiority of lactic acid measurement that involved simple peripheral venous blood draw over invasive CVP and $ScvO_2$ measurements which required central line insertions (Jones, Shapiro, Trzeciak, Arnold, Claremont, Kline, & Emergency Medicine Shock Research Network Investigators, 2010).

Jones et al. (2010) evaluated lactate clearance efficacy versus central venous oxygen saturation measurement. The results of this randomized controlled trial indicated that measurement of lactate clearance; a quicker and more non-invasive measurement can be an equally effective alternative to $ScvO_2$ monitoring in goal-directed resuscitation. In light of this evidence, the guidelines were revised and incorporated 3- and 6-hour management bundles. The updated 2012 recommendations guidelines included these 3- and 6- hour management bundles. They mandated measurement of lactate level, obtaining blood cultures prior to administration of antibiotics, administering broad-spectrum antibiotics, and infusing crystalloid fluids at a rate of 30 mL/kg for hypotension or lactate > 4mmol/L (36 mg/dL) to maintain adequate MAP within three hours from onset of sepsis. If hypotension does not respond to initial fluid resuscitation, the guideline recommended administering within six hours vasopressors (for refractory hypotension) to maintain MAP ≥ 65. In the event of persistent arterial hypotension despite volume resuscitation, or if initial lactate was > 4 mmol/L (36 mg/dL), it is recommended to monitor CVP and $ScvO_2$ and re-measure lactate if initial lactate was elevated. Targets for quantitative resuscitation included in the guidelines are CVP of > 8 mm Hg, ScvO2 of > 70%, and normalization of lactate (Haddad et al., 2015).

Dellinger, Levy, and Townsend (2010) showed an association between compliance with the SSC Sepsis Bundles and decrease in sepsis mortality. In 2012, the first national practice guidelines were endorsed by National Quality Forum (NQF) for the management of severe sepsis and septic shock (Dellinger, 2015). These NQF 2012 guidelines named Sepsis 0500 included the seven components to be completed within three- and six-hour period.

Under those guidelines, septic patients were undergoing invasive procedures such as central venous catheters (CVC) insertion that unnecessarily delayed lifesaving treatments. In 2014, the guidelines were revised in view of more new evidence based on multicenter randomized trials the ProCESS and the ARISE studies. Both trials demonstrated the lack of necessity for using invasive CVC insertion procedure for monitoring CVP and $ScvO_2$ as resuscitation measures. Given these results, NQF guidelines were revised taking into account the above findings (SSC, 2014).

The paramount underpinning of these protocols has been an aggressive and early treatment. SSC partnered with Institute for Healthcare Improvement (IHI) to incorporate the concept of sets of sepsis management strategies into the diagnosis and treatment of sepsis (SSC, 2014). The new guidelines included the same recommendation for maximum allowed time frames for drawing blood cultures and lactic acid levels, administering empiric antibiotics and providing IV fluids to patients with suspected sepsis, but did not mandate CVP and $ScvO_2$ measurements if other conditions are met. For instance, patients presenting to ED with symptoms suspicious for sepsis, should have blood drawn for serum lactate level and blood cultures, prior to administration of antibiotics and broad spectrum IV antibiotics administered within three hours of triage (time zero). However, delaying antibiotic administration in order to obtain blood cultures was not recommended. If lactate level is 4mmol/L or higher or patients are hypotensive, IV fluids are infused at a rate of 30 mL/kg. Subsequently, if patients do not respond to initial fluid resuscitation, vasopressors are administered to maintain MAP at or above 65mmHg. If no adequate response is achieved, fluid volume is re-assessed by a focused exam and two additional specific measures, which may include measurement of CVP and

$ScvO_2$, bedside cardiovascular ultrasound or dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge (Table II.2 and Table II.3) (SSC, 2014).

The guidelines were recognized and incorporated as new protocols for standards of care, and have been serving as benchmarks for quality measurements (Haddad et al., 2015). Since October 1, 2015, Center for Medicare and Medicaid Services (CMS) mandated measurement of sepsis outcomes (SEP-1). This performance measure named *Early Management Bundle; Severe Sepsis/Septic Shock* has been endorsed by NQF. Consistent with Surviving Sepsis Campaign guidelines, it assesses measurements of lactate, obtaining blood cultures, administering broad spectrum antibiotics, fluid resuscitation, vasopressor administration, reassessment of volume status and tissue perfusion, and repeat lactate measurement within three and six hours of presentation (Joint Commission, 2014).

Current Practice

The SSC has been the leader in putting forth sepsis management guidelines and best practice recommendations based on recent literature and expert opinion for decades. In October 2012 NQF endorsed the management bundles and came forth the first national sepsis guidelines in the United States (NQF 0500) that also currently serve as a benchmark for healthcare quality measures for healthcare providers and federal government (D'Amore et al., 2015). In light of new evidence published in the ProCESS and the ARISE trials; the NQF Patient Safety Standing Committee reviewed the 0500 measure in April 2014, and removed mandatory CVP and $ScvO_2$ monitoring (SSC, 2014). The protocol continues to be considered the appropriate approach to sepsis at this time and the components are used as a quality measure matrix (Table II.2 and Table II.3).

Table II.2. *SSC 3- and 6- hour Bundles*

.

To be completed within 3 hours of time of presentation*:	**To be completed within 6 hours of time of presentation**
1. Measure lactate level	5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (map) ≥65mmhg
2. Obtain blood cultures prior to administration of antibiotics	6. In the event of persistent hypotension after initial fluid administration (map < 65 mm hg) or if initial lactate was ≥4 mmol/l, re-assess volume status and tissue perfusion and document findings according to Table II.3.
3. Administer broad-spectrum antibiotics	7. Re-measure lactate if initial lactate elevated.
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L	

* "Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review (SSC, 2014, para. 3).

Table II.3. *Sepsis Reassessment*.

Document reassessment of volume status and tissue perfusion with the following:	
Either	*Or two of the following:*
• Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including	• Measure CVP
• Vital signs	• Measure ScvO2
• Cardiopulmonary, capillary refill	• Bedside cardiovascular ultrasound
• Pulse	• Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge
• And skin findings	

(SSC, 2014, para. 4)

Updated definition of sepsis.

The terms of sepsis, severe sepsis, and septic shock have been used sometimes interchangeably or inappropriately, and the actual definition of sepsis has not been revised in over a decade. Meaningful progress has been made in medicine and

technology since 2001. The sepsis definition was recently updated for the first time in 15 years by an international task force that included 19 experts in sepsis pathology, epidemiology, and clinical trials. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement. In 2016, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine released the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) re-defining sepsis (Singer et al., 2016). New criteria were added for septic shock, and the standards for rapid sepsis shock recognition were simplified. The concept of SIRS with its low specificity and high sensitivity lead to misinterpretations and discrepancies in reported incidence and observed mortality, therefore, it was eliminated (Singer et al., 2016).

According to Singer et al. (2016), too much emphasis has been placed on inflammation, which is misleading, giving the impression that the sepsis process moves in a sequence from sepsis through severe sepsis to septic shock. Singer et al. (2016) defined sepsis as a "life-threatening organ dysfunction caused by a deregulated host response to infection" (para. 4). The new definition offers better consistency for epidemiologic studies and clinical trials. It allows for more reliable uniform data collection methods for incidence and mortality reporting, and would facilitate earlier recognition of sepsis, thus better timely management of this serious condition (Singer et al., 2016).

Instead of diagnostic criteria known as SIRS, the new definition relies on known or suspected infection with a change in Sequential Organ Failure Assessment (SOFA)

score ≥ 2, or a modified quick SOFA. However, adoption of the new approach in many hospitals will likely be hindered by CMS that still uses the *SIRS-plus suspected infection* approach for description of sepsis as a benchmark for quality measures, for determining payment and compliance with performance metrics such as the SEP-1 measure.

Shortly after the publication of the new sepsis definition, Simpson (2016) expressed concern that the new definition may de-emphasize interventions at earlier stages of sepsis when the syndrome is actually at its most treatable phase. Moreover, over-simplifying the definition of sepsis, especially in light of still not precisely understood pathophysiological features that define sepsis may inadvertently cause more confusion (Simpson, 2016).

While the key is to simplify, not to further complicate, initial patient assessments in order to expedite appropriate treatment initiation, ultimately all patients with sepsis must receive optimal aggressive treatment. Regardless of definition, it is critical to continue to strive to recognize sepsis early and initiate aggressive treatments for all forms of sepsis.

Controversies of Sepsis Guidelines

Early Goal Directed Therapy: EGDT

In 2001, Rivers et al. published a single-center, randomized trial of protocolized resuscitation for patients presenting to the emergency department (ED) with a septic shock. The protocol included specific, 6-hour resuscitation algorithm, namely the EGDT. Prior to the introduction of EGDT, goal-directed therapy (GDT) was utilized for severe sepsis and septic shock in ICUs. Rivers et al. (2001) utilized a small sample of 236 patients, and the trial presents external validity threat due to single-center study, raising

concerns for generalizability of the results. EGDT targeted primarily arterial and central venous pressure and a ScvO2. SSC guidelines have endorsed EGDT since 2004, and a number of following non-randomized, predominantly before–after studies subsequently reported the benefit of EGDT on outcomes (Angus et al., 2015). However, based on new evidence, the overall effectiveness of EGDT is uncertain. Recent studies have shown conflicting results, including questionable benefits of some components of EGDT on survival rate and length of hospital stay (LOS) (Zhang, Zhu, Han, & Fu, 2015).

Recently, the efficiency of EGDT has been called into question. Three multicenter prospective randomized trials investigated the efficiency of EGDT: ProCESS (Protocolized Care for Early Septic Shock), ARISE (Australasian Resuscitation in Sepsis Evaluation) and ProMISe. (Delaney et al., 2013; Mouncey et al., 2015; Yealy et al., 2014). Results of these three multicenter prospective randomized trials demonstrated no significant decrease in sepsis morbidity or mortality when patients were treated with a strict protocol-based resuscitation strategy over usual care at the discretion of the treating physician.

The ProCESS trial evaluated whether all aspects of the original EGDT protocol (Rivers, 2001) were necessary. Thirty-one academic EDs across the United States participated in this study. A total of 1,341 patients meeting criteria for severe sepsis and septic shock were included in data analysis; 439 patients received EGDT according to the original protocol, 456 control patients received standard care, and 446 patients received protocol-based standard therapy. Despite more aggressive therapy in the protocol-based groups, there was no significant difference in 60- and 90-day mortality between the treatment groups. There were no significant differences in the incidence and duration of

cardiovascular or respiratory failure, LOS, in sepsis morbidity or mortality when patients were treated with a strict protocol-based resuscitation strategy over usual care at the discretion of the treating provider. This study outlined a protocol for administration of fluid and vasoactive agents to reach goals for systolic blood pressure, shock index, and fluid status, without mandating invasive venous access, aggressive blood transfusion, and inotropic support. A combination of EGDT and protocol based therapy offers no survival benefits as compared to not-protocol-based usual care. Generalization across various healthcare settings and outside of the United States is uncertain, and more evidence is needed (Yealy et al., 2014).

The ARISE multicenter prospective, randomized trial was designed to test the EGDT hypothesis as compared to usual care (Delaney et al., 2013). This trial was conducted from 2008-2014 at 51 tertiary care and non-tertiary care metropolitan and rural hospitals across Australia and New Zealand, with 796 patients receiving care based on the original EGDT resuscitation algorithm, and 804 control patients receiving usual care at the discretion of the treating physician. The study results demonstrated that patients in the EGDT group were more likely to receive vasopressor infusion, red-cell transfusion, and dobutamine infusion. However, despite an increased rate of aggressive therapy, there was no significant difference in 28- and 90- day mortality, hospital mortality, organ support and LOS between the two treatment groups. Adherence to the EGDT algorithm offered no survival advantage over usual care for patients presenting to the emergency department with early septic shock (Delaney et al., 2013). This trial could not be blinded, but the risk of bias was minimized through central randomization. In this study, EGDT did not reduce all-cause mortality at 90 days in critically ill patients presenting to the

emergency department with early septic shock. Therefore, the value of incorporating EGDT into international guidelines as a standard of care is questionable (Peake et al., 2014).

The ProMISe trial, a multicenter, pragmatic, open, parallel group randomized controlled trial with integrated economic evaluation was conducted in 56 hospitals in England from 2011- 2014 (Mouncey et al., 2015). The study included 1260 patients, 630 in the EGDT group and 630 receiving usual care. Interventions could not be blinded, but the risk of bias was minimized through central randomization. There were no significant differences between the EGDT and usual care groups in mortality (29.5% and 29.2% respectively) or other outcomes including serious adverse events and health-related quality of life. Moreover, on average, EGDT was associated with increased costs. Adherence to a strict EGDT strict protocol and the addition of $SCVO_2$ monitoring did not lead to improvement in outcomes. Since the death rate was lower than anticipated in this study, the outcomes may not apply to settings with higher mortality rates. Of note, decreasing mortality is a trend in recent years, and many aspects of sepsis care have evolved since the Rivers et al. (2001) study 15 years ago (Mouncey et al., 2015). This trial of early goal-directed resuscitation for septic shock raised concern for the effectiveness of this treatment; specifically, in patients with septic shock who were identified early and received intravenous antibiotics and adequate fluid resuscitation (Mouncey et al., 2015). These patients received strict EGDT protocol management and despite that, improve outcomes were not demonstrated (Mouncey et al., 2015). The aforesaid studies did not demonstrate the superiority of required use of a CVC to monitor CVP and ScvO2 in all patients with septic shock who have received timely antibiotics

and fluid resuscitation, compared with controls or in all patients with lactate >4 mmol/L (Mouncey et al., 2015).

SSC guidelines promote EGDT as means for reduction of mortality; however, conflicting results can be found in several recently published meta-analyses regarding benefits of EGDT in patients with severe sepsis and septic shock. A recent meta-analysis by Chelkeba, Ahmadi, Abdollahi, Najafi, & Mojtahedzadeh (2015) comprising RCTs performed in different geographical regions of the world and including aforementioned trials, showed that while EGDT does not significantly impact outcomes, it reduces mortality especially in low to middle-income countries (Chelkeba et al., 2015). However, the study also showed that EGDT paradoxically increases the hospital length of stay (LOS) (Chelkeba et al., 2015).

Angus et al. (2015) conducted a meta-analysis of RCTs published from January 2000 to January 2015 (N=4735 patients) to determine whether EGDT compared with usual care reduces mortality for ED patients with septic shock. The study showed that EGDT is not superior to usual care for ED patients with septic shock, as it has no effect on primary (EGDT: 23.2% versus control: 22.4%), or 90-day mortality rates, but increases ICU resources utilization (Angus et al., 2015).

Zhang, Zhu, Han, and Fu, (2015) conducted a systematic review and meta-analysis of 10 RCTs on EGDT from 2001 to 2014 involving 4,157 patients and found no significant difference in mortality between the EGDT and the control group. In this study EGDT was found to be associated with a higher mortality rate in comparison with the early lactate clearance group (RR 1.52, 95% CI: 1.06 to 2.18, $P = 0.02$). In the first six hours, compared with usual care, patients in EGDT received more inotropic agents

($P = 0.04$), fluid administration ($P = 0.05$), and red cell transfusion ($P < 0.01$). There were no significant differences in length of ICU stay ($P = 0.73$) or in-hospital stay ($P = 0.57$), ventilation rate ($P = 0.53$), and vasopressor support ($P = 0.63$). Zhang et al. (2015) point out that contrary to most recent meta-analyses, earlier studies showed that EGDT was associated with a survival benefit; however, previous studies were either retrospective or before-after studies, or meta-analyses with imperfect methodologies or designs. For example, one meta-analysis included 13 RCTs, but only 7 studies were in the EGDT subgroup; also, some included protocols that differed from the one recommended by the SSC guidelines, included non-sepsis patients, or did not include the latest ARISE study (Zhang et al., 2015).

Gu, Wang, Bakker, Tang, and Liu, (2014) included 13 trials involving 2,525 adult patients in their meta-analysis. The results suggested that EGDT significantly reduces overall mortality in patients with sepsis, especially when initiated early ($P = 0.01$); however, strong and definitive recommendations could not be made given the variable quality of the studies. Another meta-analysis of RCTs by Yu, Chi, Wang, & Liu (2016) the included five studies (N = 4,303) that utilized the EGDT protocol recommended by SSC Guidelines. Overall, there were slight decreases in mortality within 28 days, 60 days and 90 days in the random-effect model in patients with severe sepsis or septic shock receiving EGDT resuscitation; however, none of the differences reached statistical significance (Yu et al., 2016). The authors pointed out that the included trials were not sufficiently homogeneous and suggested that potential confounding factors in the negative trials (ProCESS, ARISE, and ProMISe) might bias the results and diminish the treatment effect of EGDT. Therefore, further well-designed studies should attempt to

eliminate or reduce potential sources of bias to determine if EGDT has a mortality benefit (Yu et al., 2016). Similar results and conclusions were reported in another recent meta-analysis (Xu, Yang, & Qiu, 2016) that included nine studies involving 5,202 patients with severe sepsis and septic shock.

A multivariable model was used to assess outcome differences between the serial lactate and no serial lactate cohorts to assess clinical outcomes. Lack of serial lactate monitoring was independently associated with mortality. Serial lactate monitoring is associated with an increase in crystalloid administration, resuscitation interventions, and improved clinical outcomes in ED patients with severe sepsis and septic shock (Dettmer, Holthaus, & Fuller, 2015).

EGDT has been endorsed in the guidelines of the SSC as a key strategy to decrease mortality among patients with septic shock. However, Peake et al., (2014) suggest that the value of incorporating EGDT into sepsis guidelines as a standard of care is questionable.

IV Fluids. As of today, aggressive fluid resuscitation is a hallmark of sepsis treatment and the standard of care in the management of patients with severe sepsis and septic shock (Waechter et al., 2014). Bundled with timely antimicrobial treatment, lactate measurement and blood cultures, the SSC recommends aggressive IV fluid resuscitation; specifically, intensive fluid resuscitation to achieve a CVP greater than 8 mm Hg. Waetchter et al. (2014) retrospectively analyzed data from 24 ICUs in three countries to determine how hospital mortality was influenced by combined use of fluids and vasoactive agents. Results showed that these two treatments had strong, interacting associations with mortality, and suggested that the focus during the first hour of

resuscitation for septic shock should be aggressive fluid administration, only thereafter starting vasoactive agents, while continuing aggressive fluid administration. These recommendations are based on expert opinion without adequate experimental or controlled human evidence (Hilton & Bellomo, 2012). Conversely, recent clinical trials have demonstrated that this approach does not improve outcomes for patients with sepsis (Marik & Bellomo, 2015).

Patients are often intravenously infused very large amounts of fluids (5-10 L) early in the process of sepsis treatment (Marik, 2014). Hilton & Bellomo (2012) observed that there is no evidence of research on humans that fluid resuscitation with such massive amounts of fluids (recommended at least 30 mL/kg: Grade 1C) can reliably improve blood pressure or end-organ perfusion. More recent publications suggest that this particular measure may instead be harmful, causing iatrogenic injury, that the "less is more" paradigm is perhaps more applicable in many sepsis cases, and recommend limiting IV fluids to 20-30 mL/kg in small 500mL boluses (Marik, 2014, p. 1409). While the multicenter clinical trials described previously, as well as subsequent meta-analyses of EGDT, demonstrated a lack of improvement in outcomes using aggressive fluid resuscitation, this approach is mandated by current SSC guidelines.

Marik and Bellomo (2015) argued that sepsis is primarily not a volume-depleted state; rather, sepsis is associated with arterio- and venodilation together with microcirculatory and myocardial dysfunction. Recent evidence demonstrates that most patients are poorly responsive to fluids, based on the pathophysiology of sepsis, with the loss of arterial tone, venodilation, reduced compliance, and reduced preload responsiveness (Marik & Bellomo, 2015). Almost all of the administered fluid is

sequestered in the tissues, resulting in severe edema and increasing the risk of organ dysfunction. Therefore, a physiologic, hemodynamically guided conservative approach to fluid therapy, coupled with assessment of fluid responsiveness in patients with sepsis, is likely to reduce morbidity and improve outcomes (Marik & Bellomo, 2015). Initiation of a vasopressor agent (norepinephrine) in patients who remain hypotensive (MAP <65 mm Hg) after receiving an initial bolus 20 to 30 mL/kg of crystalloid solution may be more appropriate. Furthermore, using additional boluses as needed and utilizing the passive leg-raising maneuver combined with minimally invasive cardiac output monitoring to assess volume responsiveness represents a proper, collective approach (Marik, 2014).

Antibiotics. Early studies on sepsis care suggested that with the implementation of a structured resuscitation focusing largely on IV fluid resuscitation, timely broad-spectrum antibiotics and vasopressor therapy improved outcomes (Rivers et al., 2001). In 2006, following a retrospective medical records review of 2,154 adult patients with septic shock, Kumar et al. (2006) demonstrated that an effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival. The relationship between hospital survival and duration of time between onset of recurrent or persistent hypotension and effective antimicrobial administration held whether the infection was:

- Clinically suspected or documented,
- Culture positive or negative,
- Bacteremic or nonbacteremic,
- Community-acquired or nosocomial,

- Gram-positive, gram-negative, or fungal, or
- Involving the respiratory, urinary, gastrointestinal/peritoneal and skin or soft tissue sites

(Kumar et al., 2006).

The effect also held for additional subgroups including those with neutropenia. Initiation of effective antimicrobial therapy within the first hour following the onset of septic shock-related hypotension was associated with 79% survival to hospital discharge (Kumar et al., 2006). For every additional hour of delay to effective antimicrobial initiation in the first six hours after hypotension onset, survival dropped an average of 7.6% (Kumar et al., 2006). With effective antimicrobial initiation between the first and second hour after hypotension onset, survival had already jumped to 70.5%. With the appropriate antimicrobial therapy delay to 5–6 hours after hypotension onset, the survival rate was just 42.0%, and by 9–12 hours, it was 25.4% (Kumar et al., 2006). Presented data strongly support current international guidelines and suggest that empirical, broad-spectrum antimicrobial administration should be considered an intrinsic component of initial resuscitation of septic shock.

Ferrer et al (2014) and Gaieski et al. (2010) have suggested the dominance of well-timed antibiotics administration for improved mortality in severe sepsis and septic shock; specifically, that delay in first antibiotic administration was associated with increased in-hospital mortality. These authors implied that timely administration of appropriate antimicrobials is the primary determinant of mortality in patients with severe sepsis and septic shock treated with early goal-directed therapy.

Subsequent studies have failed to demonstrate such substantial results (Puskarich et al. 2011; Sterling, Miller, Pryor, Puskarich, & Jones, 2015). Authors documented the association between timing of initial antibiotic treatment and mortality of patients undergoing sepsis protocol in emergency departments and found no association between time from triage to initial antibiotic administration and hospital mortality.

Other studies have not demonstrated any increase in mortality with a delay of antibiotic administration based on triage time. Contrary to Kumar et al. (2006), Sterling et al. (2015) found no significant mortality benefit of administering antibiotics within three hours of emergency department triage or within one hour of shock recognition in severe sepsis and septic shock.

Despite many limitations, SSC guideline specific recommendations are to administer IV antibiotics within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C), and to initiate a "Sepsis Bundle". The bundle, in addition to other requirements also entails administration of broad-spectrum antibiotics within three hours from ED triage (Dellinger et al., 2013). Whether the antibiotics were administered within specified time frame is now one of the benchmarks for the quality of care measure by Medicare. Interestingly, sepsis symptoms are often quite subtle, especially in the early stage, and in many cases, it is impossible to denote the exact time of initial sepsis onset. This may lead to inappropriate prescribing of antibiotics in order to comply with the measure.

Mostly based on limited evidence and one aforementioned retrospective study by Kumar et al. (2006), the SSC international consensus guidelines recommends administering broad-spectrum antibiotics within the first hour of recognizing severe

sepsis and septic shock (Dellinger et al., 2008, Levy et al., 2008). However, Kumar's inclusion of all ICU patients diagnosed with septic shock may have contributed to the mortality rate (56%) reported in this study, which is inconsistent with the overall mortality rate of 19% found in studies that included only ED cohort patients receiving early aggressive resuscitation (Puskarich et al, 2011).

Appropriate antibiotic therapy in patients with severe sepsis and septic shock should mean prompt achievement of antimicrobial's therapeutic concentration in blood, tissue penetration and maintenance of optimal exposure at the infection site with broad-spectrum antibiotics administered in a timely manner – as per the guideline protocol. Once the causative pathogens have been identified and tested for *in vitro* susceptibility, subsequent de-escalation of antimicrobial therapy should be applied whenever feasible (Pea, & Viale, 2009). The goal of appropriate antibiotic therapy must be pursued decisively and with continuity, in view of the ongoing problem of antibiotic-resistant infections and of the continued decrease in new antibiotics emerging (Pea, & Viale, 2009).

Despite an emphasis on the appropriateness of antibiotic administration, measuring effects of antibiotics' appropriateness and effectiveness against pathogens is only possible with known culture and sensitivity data, not usually available for 24 to 96 hours; therefore, performing this measurement in the ED is nearly impossible (Puskarich et al., 2011). Consequently, Puskarich et al. (2011) argued that it is inappropriate to require this SSC standard when determining the effect of antibiotic timing on the outcome.

Sterling et al. (2015) reported no significant mortality benefit of administering antibiotics within three hours of emergency department triage or within 1 hour of shock recognition in severe sepsis and septic shock. These results suggest that currently recommended timing metrics as measures of quality of care are not supported by the available evidence (Sterling et al., 2015).

Current SSC SEP recommendations include a list of potent broad-spectrum antibiotics that are approved for monotherapy for sepsis. According to the measure specifications, if within three hours of presentation a broad-spectrum antibiotic approved for monotherapy is not administered to a patient with severe sepsis, then a medical practitioner must consult the "Combination Antibiotic Therapy Table" to administer another approved antibiotic drug combination to satisfactorily meet the required measure (Calderwood, Coopersmith, & Gerardi, 2015). This does not promote best practice and has raised serious concerns among medical communities due to the potential unintended consequences that may result (Calderwood et al., 2015)

While many septic patients require broad-spectrum antibiotics, in some cases a more narrow-spectrum antibiotics that deliver a targeted therapy could be more appropriate if the pathogen is highly suspected or known. However, the current measures do not allow for administration of antibiotics that are not on the list, and there is a risk that medical practitioners will be inappropriately prescribing antibiotics in order to avoid payment penalties and comply with the Medicare sepsis measure (SEP-1).

Inappropriate antibiotic prescribing behaviors have led to the marked increase of antibiotic resistant bacteria and have negatively impacted LOS and patient mortality with conditions such as Clostridium difficile (C. diff) infection (Calderwood et al., 2015).

CMS considered these concerns and showed some flexibility in attempting to incorporate utilization of narrower spectrum agents for documented known sources of infection, such as C. diff colitis and type II necrotizing fasciitis.

Antibiotic Stewardship

The choice of antibiotics is determined by many factors, such as the suspected or known source of infection, the patient's immunologic status, whether the infection is nosocomial or community acquired, and knowledge of the local microbiology and sensitivity patterns (Marik, 2014). Most of the time causative organisms are not known at the time of presentation, and a broad-spectrum, empirical therapy is most appropriate, and has been shown to reduce mortality when compared with the inappropriate therapy (Marik, 2014). Once a pathogen is isolated, antibiotics should be de-escalated to more narrow-spectrum acting agents. There are instances that continuation of dual antimicrobial therapy is recommended, such as enterococcal infections, severe intraabdominal infections, severe pneumonia, pneumococcal bacteremia, neutropenia, and others. Empiric broad-spectrum antimicrobial treatment is aimed at achieving an optimal therapeutic response, thus reducing mortality; however, this can expose patients to overuse of antimicrobials and promote sprouting of multi-drug resistant pathogens.

Unfortunately, severe sepsis and septic shock are increasingly more and more frequently caused by antibiotic-resistant pathogens, including Gram-negative non-fermenters, Methicillin Resistant Staphylococcus (MRSA), Vancomycin Resistant Enterococcus (VRE), and Candida species (Zhang, Micek & Kollef, 2015). This development calls for the use of progressively more powerful empiric, broad-spectrum antibiotics, which might further promote resistance, breed "superbugs" or multi-drug

resistant organisms, and cause severe complications such as C-difficile colitis. Aside from causing delays in the delivery of appropriate antibiotic therapy (AAT), this problem may eventually pose the risk of running into unavailability of appropriate, sufficiently powerful antimicrobials (Zhang, Micek & Kollef, 2015).

The rising threat of antimicrobial resistance calls for rapid interventions with appropriate antimicrobial choices in sepsis treatment. Therefore, robust antimicrobial stewardship programs in hospitals and healthcare facilities are beneficial in attempts to combat antibiotic resistance, reinfections, and superinfections. Clinicians in collaboration with pharmacists and infection control departments should implement local strategies aimed at timely delivery of appropriate antibiotic therapy to improve outcomes and reduce the length of stay (Zhang Micek & Kollef, 2015). The hospital antibiotic stewardship program is a multidisciplinary approach and a key component to preventing increasing antimicrobial resistance (Fishman, 2006). De-escalation has been proposed as a strategy to replace empirical broad-spectrum antimicrobial treatment by using a narrower antimicrobial therapy; however, more research is needed to establish direct evidence regarding safety and efficacy of early de-escalation of antimicrobial agents for adults with sepsis, severe sepsis or septic shock (Silva, Andriolo, Atallah, & Salomão, 2013).

Timely application of AAT while avoiding the unnecessary use of antibiotics, especially broad-spectrum agents when not warranted is necessary in the treatment of infections; however, in order to successfully de-escalate antibiotics to narrower spectrum, a proper identification of causative organisms and their specific sensitivity is paramount.

Lack of ability to identify microbes is an important barrier to the effective treatment of infections. Advances in new antibiotic development along with progressing technology and evolving new rapid diagnostic techniques such as molecular diagnostics offer hope for better outcomes. The transition from traditional, culture-based diagnosing methods to molecular diagnostics will yield faster results and consequently better patients' outcomes. The advantage to such transition likely outweighs any risks; nevertheless, implementing such change has been meeting much resistance (Mancini et al., 2010).

On September 18, 2014, the White House directed the federal government to step up the fight against antibiotic-resistant bacteria. A science advisory was released, calling for reducing antibiotics overuse to preserve the efficacy of existing antimicrobials, to develop improved methods for conducting antibiotic stewardship programs in healthcare settings and to develop and promote the use of new, rapid diagnostic technologies such as molecular diagnostics and point-of-care diagnostics (Office of Press Secretary, 2014). By the end of the calendar year 2016, the Department of Health and Human Services will propose new regulations that require hospitals and other inpatient healthcare delivery facilities to implement robust antibiotic stewardship programs that adhere to best practices (Office of Press Secretary, 2014).

Molecular Diagnostics Technology

Human blood is naturally sterile. Current standard blood culture procedures consist of inoculating blood cultures bottles and monitoring for the growth of microorganisms, and any growth is assumed pathologic unless contaminated. Cultures are then Gram stained, plated to appropriate media, and allowed to grow for 24 to 72 hours or longer, with subsequent subcultures and susceptibility to antibiotics testing

results (Dekmezian, Beal, Damashek, Benavides, & Dhiman, 2015). This process creates a considerable delay in initiating AAT from the initial collection of blood sample from the patient to delivery of the most appropriate antimicrobial treatment. Newer technologies such as molecular diagnostics offer rapid identification thus more efficient infection treatment. Tests such as nucleic acid amplification tests, fluorescence in situ hybridization (FISH), and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) provide rapid identification of pathogens and codetection of key resistance markers directly from positive blood cultures (Dekmezian et al., 2015). For example, the Verigene Gram-Positive and Gram-Negative blood culture assays are approved by the Food and Drug Administration to detect common gram-positive and gram-negative organisms, as well as associated resistance markers within three hours from positive blood cultures (Dekmezian et al., 2015).

Molecular technologies have significantly shortened the time to antimicrobial isolate identification compared with conventional methods. Sango et al. (2013) evaluated the impact of *Enterococcus* identification and resistance detection using Verigene Blood Culture Gram-Positive. The intervention by an infectious disease and/or critical care pharmacist on 74 patients with enterococcal bacteremia led to a significant decrease in the meantime to appropriate antimicrobial therapy in the post-intervention group (23.4 h; $P = 0.005$) compared with the pre-intervention group (Sango et al., 2013).

Bauer et al., (2010) in a single center study, evaluated clinical and economic outcomes of rapid diagnostic polymerase chain reaction (PCR) methods on 156 patients for methicillin-resistant *S. aureus/S. aureus* bacteremia and demonstrated that the mean time to deescalate from empiric to narrow spectrum antibiotics in patients with

methicillin-susceptible *S. aureus* bacteremia was 1.7 days shorter ($P = 0.002$), the mean length of stay was 6.2 days shorter ($P = 0.07$), and the mean hospital costs were $21,387 less ($P = 0.02$) after PCR. Therefore, PCR allows rapid differentiation of *S. aureus* bacteremia, enabling timely, effective therapy and is associated with decreased length of stay and healthcare costs (Bauer et al., 2010).

A prospective randomized controlled trial evaluated outcomes associated with rapid multiplex PCR (rmPCR) detection of bacteria, fungi, and resistance genes directly from positive blood culture bottles, and demonstrated that the time from blood culture Gram stain to microorganism identification was shorter in the intervention group (1.3 hours) vs control (22.3 hours) ($P < .001$) (Banerjee et al., 2015). Compared to the control group, both intervention groups had decreased broad-spectrum antibiotic (control 56 hours, rmPCR 44 hours, rmPCR/AS 45 hours; $P = .01$) and increased narrow-spectrum antibiotic (control 42 hours, rmPCR 71 hours, rmPCR/AS 85 hours; $P = .04$) use, and less treatment of contaminants (control 25%, rmPCR 11%, rmPCR/AS 8%; $P = .015$) (Banerjee et al., 2015). Time from Gram stain to appropriate antimicrobial de-escalation or escalation was shortest in the rmPCR/AS group (de-escalation: rmPCR/AS 21 hours, control 34 hours, rmPCR 38 hours, $P < .001$; escalation: rmPCR/AS 5 hours, control 24 hours, rmPCR 6 hours, $P = .04$). Groups did not differ in mortality, LOS, or cost (Banerjee et al., 2015). Banerjee et al., (2015) reported decreased use of broad-spectrum antimicrobials with the implementation of PCR diagnostic method, and the addition of antimicrobial stewardship program enhanced antimicrobial de-escalation. Molecular diagnostics allow rapid differentiation of bacteria, enabling timely, effective therapy; moreover, it is associated with decreased length of stay and healthcare costs.

Discussion of Best Practice to Address Problems

Sepsis is a rapidly growing public health problem for Americans. There has been little change in long-term morbidity, despite changes in practice and technology. Clinicians should anticipate more frequent sequelae of severe sepsis in their patient populations, especially among elderly patients and in light of increasing antimicrobial resistance. Although overall decreasing mortality has been a trend over the past decades as many of aspects of sepsis management has changed since Rivers et al. (2001), high incidence and difficult diagnostics of sepsis remains a major problem. The management of patients with sepsis focuses on the early administration of antibiotics, IV fluids, and vasoactive agents, followed by source control; unfortunately, there is no high-quality evidence demonstrating that any of these interventions impact outcomes, especially when the interventions are bundled together (Marik, 2014). However, it is likely that timely administration of appropriate antibiotics is the single most important factor in reducing both morbidity and mortality from sepsis (Marik, 2014).

Antibiotic Resistance

Since the invention of penicillin, we had access to many reliable antibiotics, and as resistance has developed to particular drugs, new and more potent antimicrobials were almost immediately manufactured. Today, however, for some bacterial strains, the antibiotic market has shrunk, and in many cases of drug-resistant infections, the choices of antimicrobial agents are limited. There are instances of highly resistant strains that currently available antibiotics are not effective at all. Fewer antibiotics are available to treat complicated infections, and the reason for this problem is multifaceted. Inappropriate prescribing and erroneous taking of antibiotics both encourage the breeding

of resistant organisms. Pharmaceutical companies are reluctant to make new antibiotics for economical reasons. Medications are very expensive to develop and to undergo clinical trials. Those that are prescribed for life, for example antihypertensive drugs, antihyperglycemics, or antilipids can be profitable for the companies who develop them; however, antibiotics are typically used for a short period of time and once used, resistance already starts to develop. Pharmaceutical companies must be encouraged to return to the manufacturing of antibiotics to help to combat this global problem, thus initiatives are being proposed in the form of financial incentives and tax breaks.

An H.R.3539 Reinvigorating Antibiotic and Diagnostic Innovation Act of 2015 was introduced to the House Committee on Ways and Means in September 2015, Sponsored by Rep. Boustany, Charles W., Jr. (See Appendix F, Figure F.1). This bill amends the Internal Revenue Code to allow tax credits for 50% of the clinical testing expenses for infectious disease products that are intended to treat a serious or life-threatening infection, including one caused by an antibacterial or antifungal resistant pathogen, and in-vitro diagnostic devices that identify in less than four hours the presence, concentration, or characteristics of a serious or life-threatening infection (Boustany, 2015)

In March 2015, the White House released an initiative on combating antibiotic-resistant bacteria. This initiative encourages new antibiotic use protocols, antibiotic stewardship programs implementation across healthcare facilities, and better diagnostics that can quickly detect bacterial infections and multiple antibiotic resistance genes. The National Action Plan for Combating Antibiotic-Resistant Bacteria was issued and provides guidelines for this initiative. The goals are to advance the development and use

of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria, accelerate basic and applied research, and development for new antibiotics (The White House, United States Government, 2015).

Summary

Despite some differences, overall there is an agreement in the literature regarding a core sepsis approach. To reduce mortality rates, sepsis must be identified and treated as early as possible so that patients can receive optimal aggressive treatment (Lopez-Bushnell, Demaray, & Jaco, 2014). As specific recommendations evolve and change with advancing knowledge, and technology, and with emerging new evidence, the most critical aspects and the underpinning of sepsis care remains early recognition of symptoms and prompt initiation of aggressive measures with antibiotics (D'Amore, et al., 2015). The following chapter contains a description of methods utilized for this project.

CHAPTER III

METHODOLOGY

Methods

Objectives of this project were to review scientific literature for the effects of sepsis protocols on health outcomes, then conduct data analysis and compare results of two groups of patients who were hospitalized in a community hospital with the diagnosis of sepsis before and after implementation of new sepsis guidelines. The purpose of this project was to evaluate interventions in terms of utilization and effectiveness of current sepsis protocols on health outcomes, specifically on hospital length of stay, mortality, morbidity, readmissions, and appropriate antibiotics utilization; also, to assess whether implementing the mandated protocol actually influenced the timing of initiating early interventions. Further, additional goals were to examine whether recommendations for improvements are indicated, explore evidence to guide practice change, and based on the project's outcomes to validate best practice recommendation. Ultimately, the prospective, indirect aim was to determine if a change in practice is necessary.

Project Design

This evidence-based project is a descriptive, retrospective, and a pre and post measure of an intervention identified as the Sepsis Bundle protocol (SEP-1). This DNP

scholarly project was conducted at a 100-bed community hospital located in the coastal South Carolina region, which implemented the new sepsis protocol in October 2015. Through data collection and analysis, the focus of this quality improvement project was to evaluate the efficiency of interventions of current sepsis protocols and their effects on health outcomes, such as mortality, hospital length of stay (LOS), utilization of antibiotics, and morbidity among septic patients in pre- and post-implementation groups.

The pre-implementation data was collected from September 1, 2014, through September 31, 2015, and compared to the post-implementation period from October 1, 2015, through March 31, 2016. The elements of data collection were organized into objectives one to six, measured in both pre- and post-intervention groups.

(1) Objective One: Collect data and demonstrate descriptive statistics.
(2) Objective Two: Summarize findings and compare outcomes: mortality, morbidity, health outcomes, antibiotics utilization, LOS, readmission rates.
(3) Objective Three: Analyze outcomes between groups looking at selected individual variables and based on compliance with guidelines.
(4) Objective Four: Evaluate relationship between variables.
(5) Objective Five: Determine if there is a need for practice change.
(6) Objective Six: Make appropriate recommendations based on current evidence.

Sample

The unit of analysis in this project is the patient and her or his health record data. One hundred fifty-eight electronic charts of patients admitted between September 1, 2014, and March 31, 2016, were reviewed. The sample population included two groups of patients, 86 prior, and 72 after implementation of new Sepsis Bundles.

Inclusion and exclusion criteria. Inclusion criteria were comprised of adults of both genders, 18 years of age or above who had an active sepsis diagnosis at the time of presentation to the hospital, or at any time during the hospitalization, and were hospitalized within the specified time frame. To be included patients must have met the severe sepsis and sepsis shock criteria as per SEP-1 guidelines (Figure II.2).

Included were those patients with the following ICD diagnostic codes: from ICD-9 codes: 038.9 (unspecified septicemia), 995.91 (sepsis), 995.92 (severe sepsis), and 785.52 (septic shock). The ICD-10-CM codes ranged from A22 to A54 and B00.7 to B37.7, with additional multiple extension as applicable, also A41 (for other sepsis, with extensions from A41.0 to A41.9 for specific types of sepsis and due to particular or unspecified organisms). In addition, the following ICD-10-CM codes: T81.4, T88.0; T80.2 were used to generate reports for completeness. These included postprocedural sepsis, sepsis following immunization or infusion, or transfusion of therapeutic injection. Not included were codes describing bacteremia without sepsis, sepsis during labor, sepsis following abortion, neonatal sepsis and sepsis in children of any age below 18 since the target population did not include these aggregates. Appendix I lists all the ICD-10-CM codes included for the purpose of generating accurate reports. Since the new protocols were implemented on October 1, 2015, for the pre-implementation sample the case selection was from September 1, 2014, through September 31, 2015 (13 months) and for the post-implementation sample, the case selection was from October 1, 2015, through March 31, 2016 (6 months). Patients who were admitted to ACU, PCU, or ICU, were included but admitted to L&D and all neonatal and pediatric patients were excluded from the sample because they could influence or potentially introduce confounding variables.

Setting

The setting for this project was a small, community hospital located in the coastal area of South Carolina. The hospital opened its doors in 1975 as a private, 40-bed, accredited medical facility serving a small rural population. Over the years with the growing demands of the region, the hospital transitioned to a larger facility, expanded its services, and is currently certified for nearly 100 acute care beds serving the local population and visitors.

Data Collection

With the intention to accomplish the project objectives, permission for data collection, extraction from electronic medical records (EMR), and analysis was requested from the Safety Officer /Director of Risk Management of the hospital, who presented the proposal before the facility's Compliance Committee. Once permission was granted by the Compliance Officer (Appendix G, Figure G.1), a comprehensive, retrospective electronic chart review and data collection of the electronic medical records was conducted. The aforementioned facility utilizes Cerner® EMR software. For the purpose of this project, access was granted to the EMR to selected patient databases to collect necessary demographics and clinical information. The software has the capability to generate various reports; therefore, a list of patients was created by Medical Records director, de-identified and consequently received anonymous in its entirety. The list was based on diagnosis codes for sepsis using International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10-CM) (Appendix I). Once de-identified reports were received, all pertinent information was manually entered into an Excel® worksheet (Appendix J, Figure J.1). For the purpose of this project's data collection, a

spreadsheet was developed and designed to fit all data elements. The demographic information was entered from the Cerner® reports. All subjects were organized in rows by age and gender.

Unique identifiers were assigned to individual cases to facilitate analysis and to provide an opportunity for retrieval of any missing or duplicated data. Designs for both pre- and post-implementation groups data collection Excel® worksheets were identical (See Appendix J, Figure J.1 for worksheet template). For each item in data collection, a distinctive name was created, items were organized in column headings, and classified as either categorical (nominal, ordinal, dichotomous) or continuous variables (interval or ratio). Based on this classification, a specific number of sub-columns was set up for each variable to reflect the quantities of values. Some variables were answers to yes-no questions, others had numerous subcategories with possibilities to pick either only *one-out-of-all*, or *all that apply*.

Data coding was performed by establishing a numerical value for each entry options, thus all values in each subcategory of every variable had a unique number assigned that was associated with the corresponding category. For example, gender was coded as 1 = *Female* and 2 = *Male*, or number 1= answer *Yes*, and 2 = *No*. Consecutive numbers (1, 2, 3 …) were assigned to items with multiple subcategories, such as antibiotic class: 1 = antibiotic A, 2 = antibiotic B, 3 = antibiotic C, respectively. Please refer to Appendix J, Table J.1 that illustrates the template of the spreadsheet. Table III.1 below lists categories created on the worksheet for data collection, and Table III.2 shows the list of categories and subcategories of variables and outcomes measured.

Encryption of categories was conducted in a particular manner where each category had assigned a unique combination of letters that reflected in corresponding subcategory code along with previously established numerical values. For example, the category "Race" was coded *Race1-6,* and corresponding variables had numbers assigned to them as follows: 1=Caucasian (*Race1)*; 2=African American: (*Race2)*; 3=Asian: (*Race3),* 4 = Hispanic *(Race4) et cetera.* The category: "Functional status at discharge" was coded: *OutcFS 0-3,* and the corresponding subcategories received the following codes: *No change from pre-hospitalization* = 0: (*OutcFS0)*; *Worse, lost independence, declined* = 1 (*OutcFS1)*; *Better then prior to hospitalization* = 2 (*OutcFS2)*; *Deceased* = 3 (*OutcFS3).* Please refer to Appendix K, table K.1 for examples of the variables' coding system, Appendix E, Table E.1 for a list of data collection elements with corresponding codes and Appendix M, Table M.6 for the coding legend.

Table III.1. *List of Variable Categories for Data Collection*

Variable Categories	**Variable Categories**
Age	Appropriateness of antibiotics
Gender	Bundle compliance
Race	IV fluids timing and rate
LOS	First lactic acid measurement
Outcomes	Second lactic acid measurement
Mortality	Blood cultures sampling
Functional status at discharge	Duration waiting time for results
Discharge destination	Culture results
Immune status impairing diagnoses	C-diff
Comorbidities	Site of positive cultures
Sepsis cause	Identified pathogen
Hospital course	Multi-drug resistant organisms
Progression of sepsis	Antimicrobial class
Treatment with initial Antibiotics	Healthcare-acquired infection
Number of days on empiric antibiotics	Nosocomial complications
Number of empiric antibiotics	Potential costs savings
Deescalation of antibiotics	Readmitted w/in 30 days

Data were collected over 19 months from September 1, 2014, to March 31, 2016, and a total of 158 subjects were included in raw data batch, which consisted of two separate, independent samples of patients hospitalized before and after launching the new sepsis protocols. The first sample (n=86) was collected prior to the sepsis guideline implementation on October 1, 2015, and the second sample (n=72) was collected from October 1, 2015, after guideline inauguration. Only patients meeting the inclusion criteria were included in data collection and outcome measures.

Measured Variables and Outcomes

The primary goal relevant to this project was to compare health outcomes before and after implementation of new sepsis management protocols. With the intention of producing a meaningful final report, outcomes of several data elements were collected and measured in both samples (Table III.1).

Selected outcomes measured were those patients results that were expected to change after sepsis protocols were implemented. The main variables included death and survival rates, the difference in mortality between patients with sepsis and septic shock, the proportion of sepsis progressing to septic shock while hospitalized, hospital length of stay, outcomes such as patients' functional status at the time of discharge, discharge destination and readmission. These variables were arranged in categories and supporting subcategories were added as shown in Table III.2. The role of several different subcategories was to aid in explaining relationships and differences.

Table III.2. *Categories and Subcategories of Variables and Outcomes Measured*

Categories and Subcategories Of Variables And Outcomes Measured	**Categories and Subcategories Of Variables And Outcomes Measured**

• The number of days patient stayed in hospital (LOS)
• Patient survival (Mortality)
• Overall functional status at discharge (Declined, no change, improved)
• Final discharge destination
  ○ Deceased while hospitalized
  ○ Returned home with home health, or more help than prior
  ○ Went to a nursing facility, long or short term
  ○ Admitted to Hospice Care and Deceased
  ○ Prior living arrangements without change
• Immune status (impaired, normal)
• Diagnosis or conditions affecting immune status
  ○ None
  ○ Cancer (Ca)
  ○ Status post organ transplant or splenectomy
  ○ Chronic Obstructive Lung Disease (COPD)
  ○ Diabetes Mellitus (DM)
  ○ Rheumatoid arthritis or on steroids for other reasons
  ○ On chemotherapy
• Comorbidities
  ○ 0 None
	○ Vasopressors
	  ○ Focused exam
	• Fluid status reassessment
	• Number of hours pathogen was first identified as Gram-negative or Positive (preliminary results)
	• Number of hours final culture results available including sensitivity (MIC)
	• Site of original infection, port of entry
	  ○ Blood
	  ○ Urine
	  ○ Wound
	  ○ Sputum
	  ○ Stool
	  ○ CNS fluid
	  ○ C-diff infection
	  ○ Pleural fluid
	  ○ Peritoneal fluid
	  ○ Other intraabdominal infection
	• Identified pathogen or pathogens
	  ○ Gram-negative pathogen
	  ▪ Escherichia coli
	  ▪ Klebsiella pneumonia
	  ▪ Enterobacter
	  ▪ Acinetobacter
	  ▪ Pseudomonas aeruginosa
	  ▪ Proteus
	  ▪ Serratia
	  ▪ Morganella
	  ▪ Haemophilus influenzae
	  ▪ Campylobacter
	  ▪ Neisseria
	  ▪ Other
	  ○ Gram-positive pathogen
	  ▪ Staph aureus MSSA
	  ▪ Staph aureus MRSA
	  ▪ Staph coagulase (-) epidermidis

- Ca
- COPD
- DM
- Coronary Artery Disease (CAD)
- Malnutrition
- Alcohol (ETOH) abuse, chronic
- Readmitted, recurrent infection
- History of previous sepsis
- History of multi-drug resistant infection
- Underlying dementia
- End Stage Renal Disease (ESRD), on dialysis
- Obesity
- Congestive Heart Failure (CHF)
- Peripheral Vascular Disease (PVD)
- Other

- Initial presentation
  - Sepsis
  - Severe sepsis
  - Septic shock
- Acute mental status change (AMS)
- Sepsis cause
  - Pneumonia
  - Urinary tract infection (UTI)
  - Pyelonephritis
  - GI/intraabdominal
  - Skin (cellulitis)
  - Post-surgery complications
  - Wound infection
  - Meningitis
  - Neutropenic fever
  - Fever of unknown origin (FUO)
    - Streptococcus pneumococcus
    - Strep viridians
    - Strep group A pyrogens
    - Corynebacterium
    - Enterococcus faecium
    - Enterococcus faecalis
    - Clostridium
    - Corynobacterium
    - Bacillus
    - Other
  - Atypicals
    - Mycoplasma
    - Chlamydia
    - Ricketts
  - Viral
  - Fungal
  - MDR Organisms
    - MRSA
    - VRE
    - CRE
    - C-diff
    - ESBL
    - Other
- Antimicrobial class
  - Penicillin (PCN)
  - Extended PCN (Zosyn)
  - B-lactamase inhibitor PCN (Unasyn)
  - Cephalosporin 1st generation
  - Cephalosporin 2nd generation
  - Cephalosporin 3rd generation
  - Cephalosporin 4th generation
  - Cephalosporin 5th generation (Ceftaroline)
  - Fluoroquinolone 2nd generation (Cipro)
  - Quinolone 3rd generation (Levaquin/Moxifloxacin)
  - Macrolides
  - Tetracycline
  - Sulfonamides
  - Carbapenems
  - Monobactam (Aztreonam)

    - Bacteremia without identified source
    - Osteomyelitis
- Hospital course
    - ICU with vasopressors
    - Mechanical ventilation
- Progression of sepsis
    - Severe sepsis progressed to septic shock despite treatment
    - Better, status did not deteriorate during hospitalization
- Antimicrobial stewardship
    - Deescalation of antibiotics
    - Number of antibiotics
    - Number of days on antibiotics
- Sepsis protocol compliance
    - Initiation of treatment with antibiotics, timing
    - IV fluids infusion rate and timing
    - Lactic acid sampling, results and timing
    - Blood culture sampling, results and timing
    - Glycopeptide (Vanc)
    - Liptopeptide (Cubicin/Dapto)
    - Oxazolidinone (Zyvox/linezolid)
    - Lincosamide (Clindamycin)
    - Other antibiotics (Tigecycline)
    - Nitroimidazole (Flagyl)
- Other Treatment
    - Antifungal (fluconazole)
    - Antiviral
    - Other atypical
- Appropriate antibiotic for culture results
- Healthcare-acquired infection
- Hospital complications
    - C-diff
    - MDR organism
    - Surgery
    - Neutropenia
    - Coagulopathy
    - Abscess
    - Renal failure
    - Respiratory failure
    - Multisystem failure
    - Cardiac complications
- Potential costs savings
    - On LOS
    - On antibiotics
- Readmitted within 30 days

Strategies to Reduce Barriers

Facilitators and barriers were identified and examined. No major impediments were identified to data collection and analysis with the exception of the time required to complete this project. Elements that could have affected outcomes of this project may be possible flaws in data based on inaccurate documenting of clinical findings in EMR. Other issues affecting outcomes are noncompliance with guidelines, infeasible approaches, and ineffectiveness of some components of the guidelines along with long waiting time for culture results possibly leading to inappropriate antibiotic prescribing. Managers, as well as staff in general, are often wary of challenges and risk averse, therefore resistant to change.

A number of barriers exist to the adoption of recommendations resulting from the data analysis and evidence review, including the absence of an innovation culture in the organization, lack of abundance of supportive evidence, financial constraints, and a budget that does not allow additional spending and administration that does not encourage innovation or change. To overcome barriers, the project's findings have to be integrated with collaborative sepsis team efforts to improve sepsis outcomes in this setting, and use data to validate best practice recommendations. To help reduce barriers to change, forming a team of supportive colleagues who take ownership of quality and safety initiatives is critical to successful implementation of evidence-based practice and ongoing quality improvement.

Instruments

Data was collected retrospectively in a systematic fashion as described above utilizing electronic tools. Three major instruments were used including EMR Cerner®,

Microsoft® Office Excel® 2007 program, and Statistical Analysis Software (SAS®) statistical software. The Cerner® was utilized for generating reports, access to clinical records, review and collection of pertinent information for this project.

Data was organized, sorted and statistically described using Excel® worksheet for editing, formatting, developing graphs and charts, also its spreadsheet functionality such as descriptive statistics and basic mathematical and sorting tools and formulas. Finally SAS® was used for statistical data analysis of both the pre-implementation and the post-implementation samples.

Procedure

The purpose of this comprehensive retrospective records review and data collection for this project was to analyze differences in outcomes before and after the introduction of the new sepsis protocol. Eighty-six electronic charts were reviewed in the pre-implementation data set (n = 86), and 72 in the post-implementation data set (n = 72)

Charts were reviewed in the context of septic patients' outcomes based on timely approaches and administration of mandated treatments as opposed to the standard practice. Variables such as mortality, LOS, morbidity, patients' outcomes including loss of function, hospital complications, AAT, MDR infections, and readmissions strongly affect outcomes, and were the principal aspects analyzed in this project. In addition, compliance with each component of the new Sepsis Bundle protocol is now a benchmark for the quality measure and mandated by Medicare.

After data entry was completed, data quality and reliability were examined through a series of procedures including random re-checks of all the records, and inspection of each element for the accuracy of data entry and correct coding utilizing

spreadsheet's sorting functionality. Data was double-checked for errors and omissions by hand, also using the spreadsheet functionality all numerical values were sorted and checked for accuracy of data entry. Less than 1% of records within the entire collection were found to be missing or incorrectly coded, and errors were corrected and re-checked for accuracy based on expected ranges of values in each category before data was analyzed.

Data Analysis Methods. This post-hoc analysis consisted of comprehensive literature review, retrospective data collection and analytical approach to data. Initial descriptive statistics were run using Excel® functions within the spreadsheet such as AVERAGE (arithmetic mean), RANK (list of values ranked by order relative to other values), STDEV (sample standard deviation), SUM (sum of numbers in a range of cells), COUNTIF (count of numbers that meets given conditions), MAX, MIN (largest and smallest values), MEDIAN (middle number), MODE (most frequently occurring value), QUARTILE, SUMIF (sum given specified condition), CORREL (correlation coefficient between two data sets), PEARSON (Pearson correlation coefficient), PERCENTILE, and T.TEST.

Sorting and calculations performed on the raw data allowed formatting of data elements for appropriate entry into the statistical software for data analysis. Data from the two groups (pre-implementation and post-implementation) were arranged and organized in sets by age, gender, LOS, mortality, hospital course, discharge status and other outcomes, then ranked accordingly, thus prepared for processing by statistical software. Subsequently, preliminary descriptive statistical values obtained using Excel®

functions were plugged into the Statistical Analysis Software (SAS®) for detailed analysis.

The frequency tables were developed, the t-test, and means procedures were used for descriptive statistical analysis and data distribution analysis. Pearson's Correlation Coefficient and Spearman's Correlation Coefficient procedures were used for comparison of outcomes.

Figures are presented in the following chapter illustrating the descriptive statistics and data analysis; further, data analysis outcomes are shown and demonstrate whether there was a statistical difference in comparing variables in categories and subcategories between pre-implementation and post-implementation groups. Inferential data is presented in tables and graphs in the following chapter. P value at the level of $p < 0.05$ is used to indicate a statistically significant difference.

Human Subject Protection

The purpose of this scholarly project was to evaluate the effectiveness of current sepsis protocols on patients' outcomes. This project included health data of human beings, which involved electronic chart reviews, health record information extraction, and analysis; however, as a Quality Improvement project specific to the setting and without intent to produce generalizable results, no Institutional Review Board review was necessary. A request for permission to use data from EMR was filed with the Safety Officer /Director of Risk Management and granted by the Compliance Officer of the hospital (Appendix G, Figure G.1).

The collection of data required to some degree participant identification, but only available to the author, an employee of the institution, in the form of raw data. No

identifying data was collected or stored and individual cases were assigned unique identifiers for purposes of data analysis. Data was located on a password-protected computer and the access to this information was only through the secure password-protected server.

This Quality Improvement project does not involve any known risks to subjects. The outcomes of this project or the entire process of data collection and analysis do not affect the rights or welfare of the subject. All evaluation information was kept anonymous and was disseminated by aggregate data only. Obtaining consents was not indicated and it would be impractical to carry out this project if consents were required; further, having written consents would risk potentially linking participants with records in the final project. There were no known physical, psychological, or social risks involved during the implementation of this intervention. The project involves a considerably small sample; however, data was only reported in aggregate, thus identification of individual subjects is implausible

CHAPTER IV

RESULTS

Project Findings

Description of Sample

This project was designed to compare outcomes of patients with sepsis treated in a hospital before and after the launching of the newest sepsis guidelines, to evaluate the effectiveness of the guidelines, and based on results, to assess the need for improvement and practicability of recommending practice change. The study was completed at a medical center located in the coastal South Carolina region, and utilized the EMR for retrospective data collection. A total of 158 electronic charts were reviewed, which included charts of 86 patients with sepsis who were treated prior to the newest mandatory Sepsis Bundles were made a part of the hospital protocol (pre n=86), and 72 charts of septic patients who were treated after the protocols were implemented (post n=72).

Data including descriptive statistics for the relevant variables and outcomes are displayed below in tables, charts and graphs. Table IV.1 shows percentages of all patients admitted with sepsis, patients who developed septic shock, and those who had severe sepsis in the pre-implementation group as compared to the post-implementation group.

Table IV.1. *Incidence of Sepsis, Severe Sepsis and Septic Shock*

Sepsis, incidence	**Pre (n=86)**	**Post (n=72)**
	%	%
Septic Shock	41	31
Severe Sepsis	42	58
Sepsis NOS	17	11

* Note: some patients had more than one diagnoses

The major finding in this data set is that while 16% more patients with severe sepsis were treated in this hospital prior to Sepsis Bundle implementation than after, 10% fewer patient presented with or developed septic shock.

Demographic Data

Demographic data is displayed below in Table IV.2. In the pre-implementation sample, there were 42% females and 58% males, 91% of Caucasians, and 7% African Americans, as opposed to the post-implementation sample of 44% females and 56% males, 86% Caucasians and 8% African Americans. The average age of all participants was 74.45 years. Data shows that 43% of patients were female and 57% were male, and the majority of patients in both groups were Caucasian (88.5%).

The mean age of the entire sample was 74.42 years, and the overall range was 23 to 97 years. The age range in the pre-implementation group was from 23 to 97 years, and in the post-implementation group, it was 33-97 years. The mean age in the pre-implementation group was 72.14, and post-implementation was 76.71 years. The difference in age between the two groups was 4.57 years ($p<0.05$).

Table IV.2. *Demographics. Distribution of Age, Gender and Race by Group*

Demographics	**Pre (n=86)**	**Post (n=72)**
	%	%
Gender		
Female	42	44
Male	58	56
Race		
Caucasian	91	86
African American	7	8
Hispanic	2	6
Asian	0	0
Other	0	0
Age	years	years
Age, average	72.1	76.8

Distribution among genders is not equal among males and females in both groups. The male gender predominance is observed in both groups. Sixteen percent more men than women were treated for sepsis in the pre-implementation group, and 12% more men than women were treated in the post-implementation group. A disproportional percentage of Caucasians is noted in both groups as compared to other races. Ninety-one percent of patients hospitalized with sepsis in the first group were Caucasians, as compared to 9% of all other races combined in the same group. Similarly, 86% of patients were Caucasians, as compared to 14% of all other races combined in the second group

Figure IV.1 shows two histograms displaying the distribution of ages of the patients hospitalized with sepsis in each implementation group.

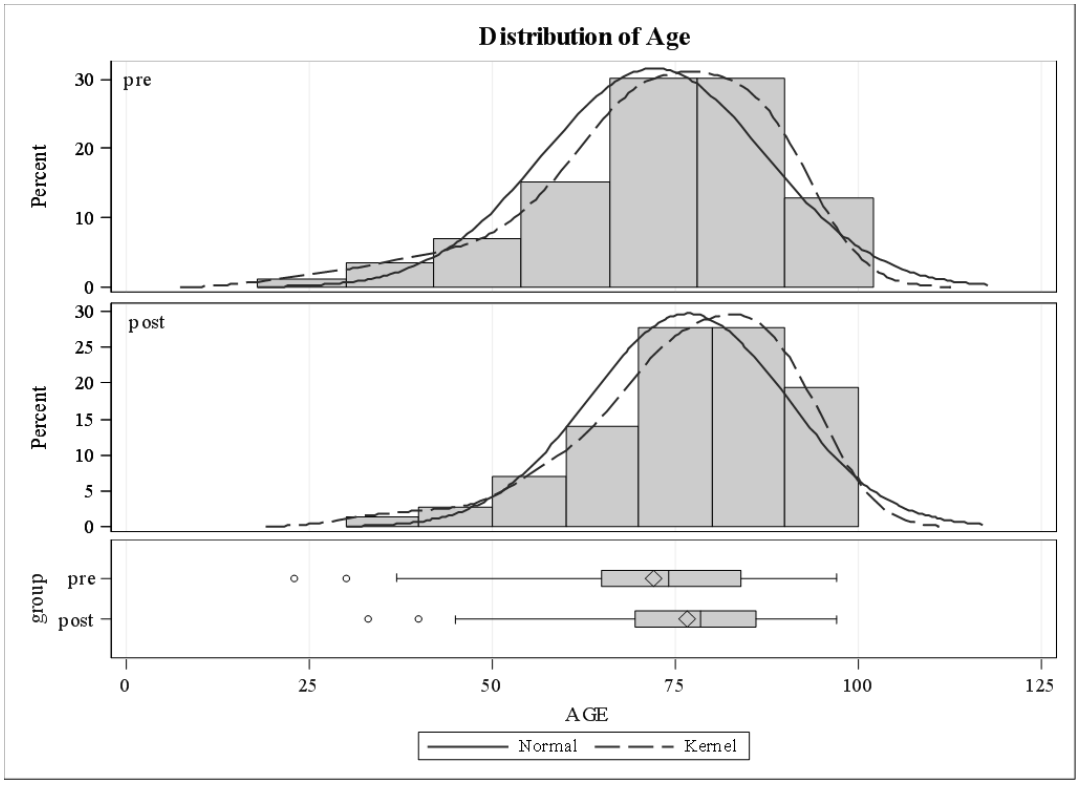

Figure IV.1. Distribution of Age by Group

Both groups' characteristics in reference to age distribution are similar and representative of the known population in this setting; however, what stands out in this figure is that the post-implementation group was older.

Descriptive data consisted of individual observations collected for the project objective (Objective One) also included mortality, LOS, most common antibiotic prescribed, antibiotic treatment duration and most frequently occurring causative pathogens.

Mortality Rate and Length of Stay

Overall hospital mortality rate for patient population carrying sepsis diagnosis and hospitalized within the specified time period from September 1, 2014, to March 31, 2016, was 31.65% (Table IV.3).

Table IV.3. *Mortality by Group*

Mortality	**Pre (n=86)**		**Post (n=72)**	
Mortality by group	Frequency	%	Frequency	%
Alive	51	59.3	57	79.17
Deceased	35	40.7	15	20.83

Mortality, overall, both groups

Outcome	Frequency	Percent
Alive	108	68.35
Deceased	50	31.65

The mortality rate for the pre-implementation group was 40.7% with a survival rate of 59.3%, and in the post-implementation group, the mortality rate was 20.83% with a survival rate of 79.17%. A difference of 19.87% in mortality rate was noted between the two groups.

Table IV.4 shows septic patients' mortality in relation to age and LOS. A t-test of mortality with regard to age in both pre- and post-implementation groups (Table IV.4) showed that the average age of patients who were deceased was 78.16 years and the average age of survivors was 72.4 years ($p<0.05$).

Table IV.4. *Mortality by Age and LOS*

	Alive			**Deceased**			**T-test p-value**
Variable	*N*	*Mean*	*SD*	*N*	*Mean*	*SD*	
Mortality by age	108	72.40	14.8103	50	78.16	13.25	<0.05
Mortality by length of stay	108	7.06	4.89	50	7.08	5.83	0.9

The difference in the LOS between the patients who survived and who were deceased (0.024 days) was not statistically significant (p=0.9). More details regarding mortality and LOS are shown in the Appendix M. Table M.1 and M.2 and Figures M.1 and M.2 in Appendix M. Data in charts graphically demonstrate the distribution of mortality by LOS and LOS by age between groups.

Table IV.5 shows the difference between means of ages of septic patients hospitalized before and after implementation of the sepsis protocol. The mean age in the pre-implementation group was 72.14 years and in the post-implementation was 76.71 years; resulting in a statistically significant age difference of 4.57 years between the two groups (p <0.05).

Table IV.5. *T-Test: Difference Between Groups*

	Pre-implementation			**Post-implementation**			
Variable	*N*	*Mean*	*SD*	*N*	*Mean*	*SD*	**p value**
Age	86	72.14	15.17	72	76.71	13.44	<0.05
LOS	86	7.38	5.46	72	6.68	4.85	0.4
Number of prescribed empiric IV antibiotics per patient per stay	86	3.03	1.17	72	3.17	1.41	0.5
Number of days on empiric IV antibiotics	86	6.62	4.33	72	6.94	5.02	0.66
Number of hours until pathogen was identified	82	33.70	12.63	71	31.59	12.00	0.3
Number of hours final results of cultures are known	82	64.68	19.97	71	69.59	13.33	<0.05

The average LOS for the pre-implementation group was 7.38 days and post-implementation was 6.68 days. A minimum number of days patients were hospitalized was one day for both groups. The maximum number of days for the pre-implementation group was 26 days, and for the post-implementation group was 27 days. The difference in LOS between the two groups was 0.7 day (p=0.4), which while statistically insignificant, may represent a considerable difference in resource consumption for hospitals (Table IV.5). The average number of empiric antibiotics prescribed before the launch of new guidelines was 3.03 with minimum 0 and maximum 5, as opposed to the average number 3.17, minimum 1 and maximum 7 after guidelines were in place, and the difference was 0.13 (p=0.5), (Table IV.5). The average number of days each patient received empiric antibiotics in the first group was 6.62 and in the second group 6.94. The minimum number of days was 0 and maximum 22 for the pre-implementation group; for the post-implementation, 1 and 27 days, respectively. With a 0.33 day difference, this finding is also not significant (p=0.66), (Table IV.5).

Waiting Time for Blood Cultures

The number of hours of waiting time before the causative pathogen was first identified in a cultured specimen, and the number of hours before the final results for culture and sensitivity were available are shown in Table IV.5. The average waiting time for the initial identification was 33.7 hours for the first group and 31.59 hours for the second group, with a minimum of 2 hours, and a maximum of 72 hours respectively. The difference was 2.1 hours (p=0.3).

The final culture results were available, on average, 64.68 hours after specimen collection before guidelines implementation, and 69.59 hours in the post-implementation

group, with a minimum of 2 hours and a maximum of 100 hours in the first group, and a minimum of 40 and a maximum of 92 hours in the second group. The calculated difference for this measure between the two groups was 4.91 hours and the difference was statistically significant (p=0.05, Table IV.5). Additional data regarding the most frequently used antibiotics and their utilization in sepsis is presented in Appendix M, Figure M.3, and Table M.3.

For supplementary and supportive purposes to aid with the explanation of results, ancillary data was collected regarding sepsis-related conditions, including the most frequently occurring disease associated with sepsis as well as the most frequent causative organisms, including C. diff. and MDR organisms. Pneumonia and urinary tract infection (UTI) were the most frequently occurring conditions for both groups. Escherichia coli (E. coli) bacterium and Candida fungus were the most often identified pathogens isolated in septic patients (Appendix M, Figure M.4, Table M.4 and Table M.5).

For Objectives Two and Three, outcomes were summarized, and then analysis was conducted while the pre-implementation and post-implementation groups' outcomes were compared. Compliance with each element of the new sepsis guidelines was measured in the post-intervention group and compared to prior performance.

To achieve a clearer picture of the Sepsis Bundle's impact on health outcomes, additional data were gathered, including patient's condition upon discharge from the hospital, discharge destination, and readmission rates. For Objectives Four and Five, results were examined for relationships, similarities, and differences, and conclusions were made in efforts to answer the PICO question guiding this scholarly project.

An additional secondary, but noteworthy, finding was the occurrence of a mental status change in older patients with sepsis. Seventy-six percent of patients with sepsis experienced mental status changes. The average age of those with acute delirium was 79 years as opposed to 69 years among those without acute confusion in the post-implementation group. Similarly, 7.9 years difference in age between patients with and without mental status change associated with sepsis was noted in the pre-implementation group.

Health Outcomes

This project aimed to answer the PICO question: In adult patients presenting with sepsis before and after October 1, 2015, does implementation of a new sepsis protocol reflect in improved outcomes such as reduced hospital LOS, decreased mortality, morbidity, readmissions, and appropriate antibiotics utilization, and does it result in initiating early treatments as compared to previous approaches?

Morbidity. Table IV.6 shows outcome variations between both groups in patients' mortality, functional status change at the time of discharge, the difference in required level of care at discharge, as well as hospital course, in-hospital complications, and readmissions. Additionally, differences in means of patients' ages in each group in relation to functional status at discharge and required level of care at discharge were taken into consideration.

Table IV.6. *Outcomes of Patients with Sepsis*

Sepsis Outcomes	**Pre (n=86)**	**Post (n=72)**
Functional status at discharge	%	%
Better	2	0
Same	19	15
Worse	38	64
Deceased	40.7	20.83
Discharged destination	%	%
Prior living arrangements	23	21
SNF	12	19
Higher level of care/ transfer to tertiary hospital	5	1
Home Health	20	32
Hospice	9	6
Hospital course		
Nosocomial/healthcare acquired infection	13	36
ICU, intubated	38	10
ICU, pressors	35	43
PCU	50	47
Of all pneumonia cases, HAP	13	47
Of all pneumonia cases, readmitted	15	56
Readmission among patients with sepsis	17	47
Sepsis progressed, worsened during treatment	46	28
Septic shock-only mortality	57	36
Sepsis mortality	40.7	20.83
Average age of those with functional status change	years	years
Better	71.5	n/a
Same	71.1	61.8
Worse	64.6	78.6
Deceased	77.6	81.7
Average age of those discharged to other settings		
Prior living arrangements	62.3	65.1
SNF	78.4	81.8
Deceased	75.3	81.7
Higher level of care/ transfer to tertiary care	58.3	72.0
Home Health	74.1	76.7
Hospice	81.1	85.0

Figures in Table IV.6 show differences in patient outcomes prior to and following implementation of the sepsis protocol. Sixty-four percent of sepsis survivors in the post-implementation group experienced worsening of their functional status, as compared to 38% in the pre-implementation group, at the same time observing 20.83% mortality in the post-implementation group and 40.7% in the post-implementation group. This is in the context of 57% and 36% mortality rate of patients with septic shock for pre-implementation and post-implementation groups and respectively.

The average age of patients experiencing worsening of their functional status in pre- and post-implementation groups was 64.6 and 78.6 years, respectively. Other noteworthy findings include a higher percentage of patients who lost or had a decrease in independence after hospitalization (26%) and a higher nosocomial (hospital acquired) infection rate (23%) in the post-implementation group. In addition, a much lower percentage of patients requiring intubation and ventilator support (28%) and a higher incidence of sepsis associated with pneumonia were observed in the post-implementation group. A substantial increase in nosocomial complications was noted (13%), and the leading cause was healthcare-acquired pneumonia, which increased from 13% to 47%. Of all deceased patients, over 70% had sepsis caused by pneumonia. The readmission rate increased 30% with an increase in pneumonia cases as a major cause for readmissions. While the readmission rate went up from 17% to 47% in the post-implementation group, the mortality rate among those who were readmitted decreased from 78% to 29.4%. Protocol compliance and antibiotic utilization are addressed in Tables IV.7, IV.8, and IV.9.

Utilization of Antibiotics and the Sepsis Protocol Data

Table IV.7 shows the percentage of patients who had antibiotics administered within the first three hours from the onset of sepsis, the percentage of the number of antibiotics deescalated during hospitalization, as well as the percentage of the times that the initially prescribed antibiotic turned out to be inappropriate based on culture results.

Table IV.7. *Antibiotics Prescribing Trends*

Prescribing trends	**Pre (n=86)**	**Post (n=72)**
	%	%
Antibiotics deescalated	43	65
Inappropriate antibiotic choice for culture results	31	58
Antibiotic administered within 3 hrs	72	58

In the post-intervention group, there was a 22% increase of antibiotics which had been deescalated from empiric to a narrower spectrum antibiotics. There was also a 27% increase in inappropriate antibiotic choice for culture results, and a 14% greater delay in antibiotics administered within three hours in the post-implementation group as compared to the pre-implementation group.

The mean LOS for patients' who received appropriate antibiotic therapy (AAT) was 5.8 days and patients who received inappropriate antibiotics had an average hospital stay of 9.1 days ($p<0.0001$). Among those who received AAT, the difference in LOS between the two groups is 3.33 days (Table IV.8).

Patients who received AAT on time received empiric IV antibiotics on average for 5.84 days, but those who had antibiotics prescribed inappropriately received empiric IV antibiotics on average for 8.33 days($p<0.001$). Patients who were treated for sepsis with inappropriate antibiotics received on average 3.82 empiric antibiotics during the

hospitalization, and those on AAT received on average 2.67 empiric antibiotics (p<0.0001). The inappropriateness of antibiotics was determined based on final culture results if shown the treatment was ineffective or inappropriate against causative organisms The difference in days on empiric antibiotics was 2.48 day between groups (Table IV.8).

Table IV.8. *Antibiotic utilization*

	Yes			**No**			**p-value**
Variable	*N*	*Mean*	*SD*	*N*	*Mean*	*SD*	
Received AAT (yes, no)/ LOS	96	5.80	4.14	61	9.13	5.99	<0.0001
Received AAT (yes, no)/ Number of days on empiric IV antibiotics	96	5.84	3.82	61	8.33	5.36	<0.001
Received AAT (yes, no)/ Number of prescribed empiric IV antibiotics	96	2.67	1.00	61	3.82	1.32	<0.0001

The difference in an average number of empiric antibiotics prescribed per patient between two groups was 1.15 (Table IV.8). Additional data regarding distribution and frequency of individual antibiotic utilization for both groups can be found in Appendix M, Figure M.3, and Table M.3.

Sepsis protocol utilization. Utilization of the new sepsis protocol was measured using the elements of the Sepsis Bundle guidelines for early management, as shown in Table IV.9. The percentages of patients receiving treatments on time according to the protocol were measured in both pre- and post-implementation groups.

Table IV.9. *Sepsis Protocol Compliance: Early Interventions*

Sepsis Protocol Compliance: Early Interventions	**Pre (n=86)**	**Post (n=72)**
	%	%
1st Lactic Acid measures within 3 hrs	73	90
2nd Lactic Acid measured within 6 hrs when indicated	11	49
Lactic Acid results > 2	60	65
IVF initiated per protocol	58	65
Blood cultures drawn before antibiotic and within 3 hrs	80	80
Antibiotic administered within 3 hrs	72	58
Vasopressors per protocol	78	81
Focused exam	n/a	45

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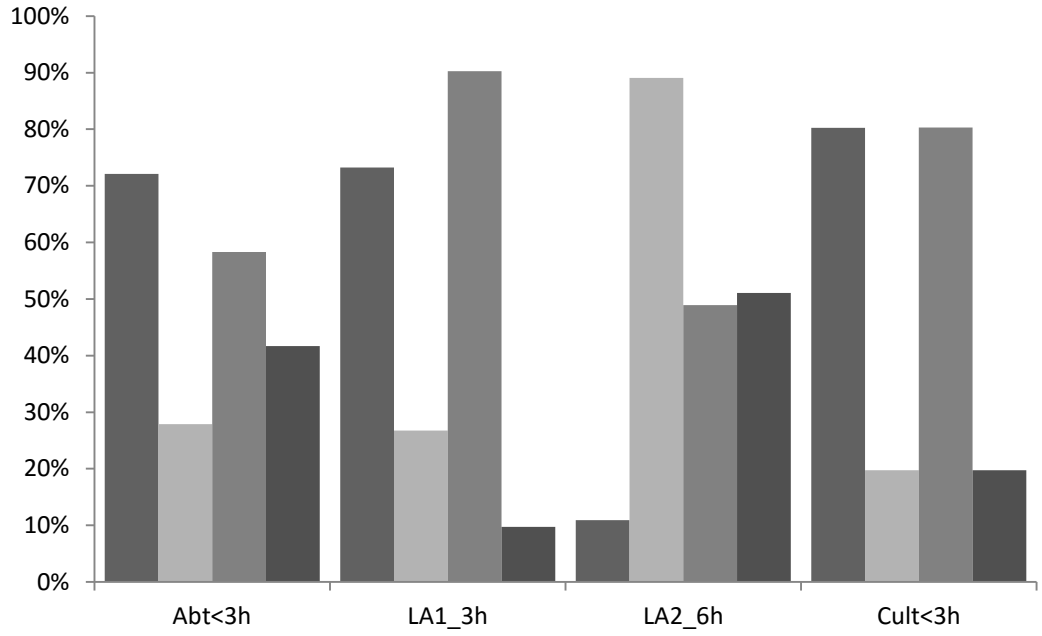
Noteworthy is the change in the collection of the lactic acid performance measure between the two groups from 73% to 90% compliance obtaining the first specimen and from 11% to 49% compliance obtaining the second lactic acid specimen. There was no change in drawing blood cultures before and after implementation of sepsis protocols, but the administration of antibiotics within the first three hours from sepsis onset dropped from 72% to 58%.

Figure IV.2 is a graphical display demonstrating utilization of the sepsis protocols including the early interventions: receiving antibiotics within three hours from initial sepsis onset, having blood specimen drawn for blood cultures, first lactic acid level within three hours, and second lactic acid level within six hours of sepsis presentation. The chart shows a comparison of those elements between both groups.



		Abt<3h	LA1_3h	LA2_6h	Cult<3h
		%	%	%	%
Pre	Yes	72	73	11	80
	No	28	27	89	20
Post	Yes	58	90	49	80
	No	42	10	51	20

Figure IV.2. Sepsis Guidelines Compliance.
*(Abt<3h: antibiotic administered within three hours from presentation; LA1_3h and LA2_6: lactic acid collected within three and six hours respectively; Cult<3h: blood cultures were drawn within three hours).

The first set of columns in Figure IV.2 represents the percentage of patients who either received or did not receive antibiotics within three hours from sepsis presentation in the pre-implementation group, followed by columns representing the post-implementation group. This distribution demonstrates a decrease in the percentage of patients who received antibiotics on time after implementation of the sepsis protocol. On the contrary, the percentage of patients having lactic acid drawn within the first three and six hours increased after the new sepsis guidelines were put in place. The timing of obtaining blood culture specimen did not change between groups.

Summary of outcomes. Figure IV.3 is a graphical display demonstrating patients' outcomes, specifically patients' condition and functional status at the time of discharge, as well as discharge destination. The chart shows a comparison of those elements between both groups.

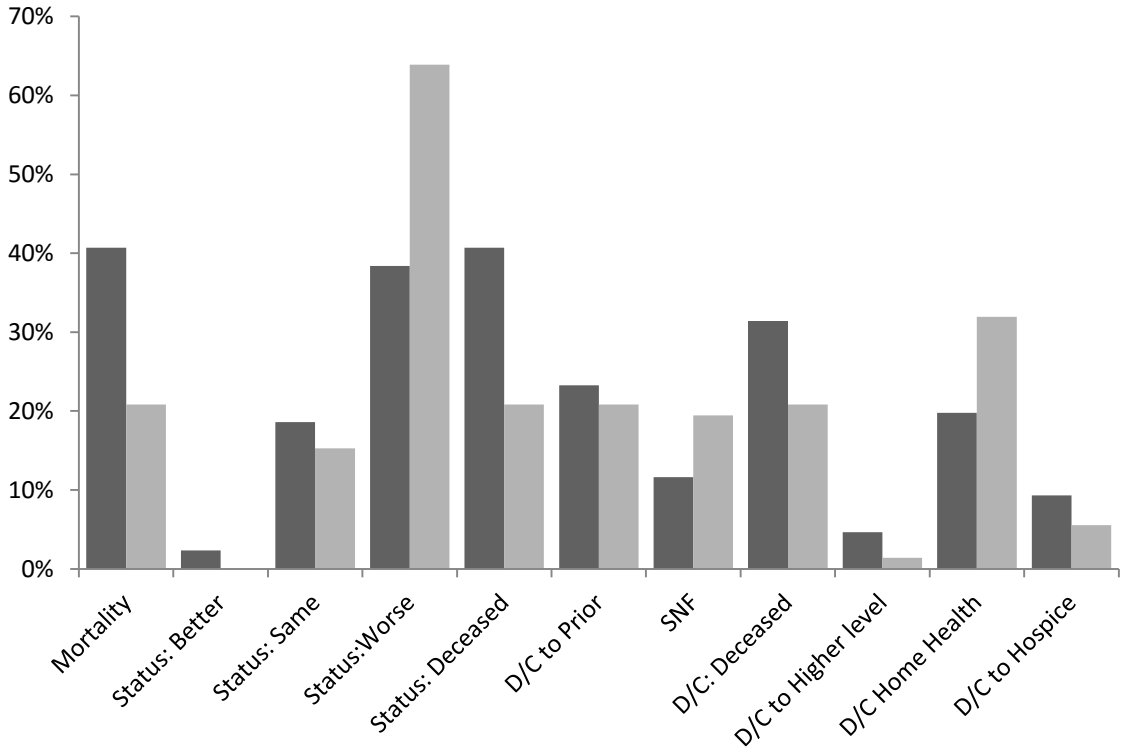


Figure IV.3. Patients' Outcomes After Discharge Chart – Comparing Both Groups.
*(Dark gray bar = pre-implementation group; light gray = post-implementation group)

The most important differences within Figure IV.3 are the variations between groups in patients' mortality and health at the time of discharge from the hospital. While mortality improved in the post-implementation group, there were considerably more patients whose health status worsened and who were consequently discharged to higher levels of care than before admission, whether it was a skilled nursing facility or home health agency assistance at home.

Relationships between variables. Multiple variables including age, LOS, patients' outcomes at discharge, initial presentation, empiric antibiotic utilization, and waiting time for culture results were compared to each other to investigate the dependence between them. The table below shows the matrix containing correlation coefficients between the possible pairs of variables (Table IV.10) accompanied by the scatter plot for visualization of the matrix (Figure IV.4).

Table IV.10. *Correlation Coefficients among Both Groups Outcomes*

	Age	*LOS*	*OutcmFS*	*IniPre*	*AbtEmpD*	*AbtEmp*	*CulthrID*	*CulFIN*
Age	1							
LOS	-0.0245	1						
OutcmFS	0.2363	0.1369	1					
IniPres	-0.0847	0.1153	0.3524	1				
AbtEmp#D	-0.0924	0.8797	0.0385	0.0806	1			
AbtEmp#	-0.0434	0.4931	0.0821	0.1367	0.5192	1		
Cult#hrID	-0.0749	0.1005	0.1785	-0.0093	0.0835	0.1071	1	
Cltr#hrFIN	-0.0320	-0.0549	0.0152	-0.0170	-0.0145	0.0716	0.4358	1

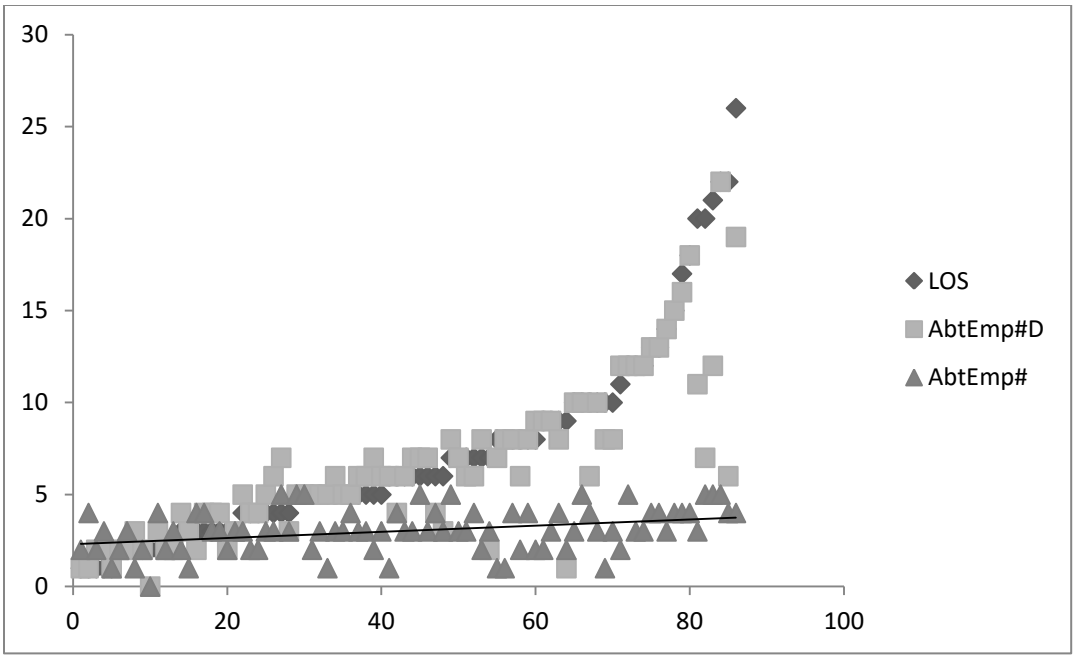


Figure IV.4. Correlation Coefficients among Both Groups Outcomes Scatter Plot.

The scatter plot above (Figure IV.4) corresponds to items included in the correlation coefficient matrix in Table IV.10. It demonstrates the strongest relationship between the LOS and the number of days empiric antibiotics were prescribed and between the LOS and the number of antibiotics prescribed. The correlation between these variables is positive, meaning that the longer the LOS, the more empiric antibiotics were prescribed, and empiric antibiotics were received for a greater number of days. Table IV.10 shows a very strong positive correlation between the duration of treatment with antibiotics (AbtEmp#D) (0.8797) and the number of empiric antibiotics prescribed (AbtEmp) and the patient's LOS (0.4931). A positive but weaker relationship exists between patients' ages and declined functional status (OutcmFS) at the time of discharge (0.2363), as well as patients' condition at the time of initial presentation and discharge (0.3524). The correlation between age and LOS is negative and extremely weak, almost

negligible. (-0.0245). A strong positive correlation exists between the number of empiric antibiotics prescribed and the duration of treatment with antibiotics (0.5192).

Summary

The focus of this project was retrospectively evaluating outcomes of patients with severe sepsis before and after implementing the Sepsis Bundle. The results of this analysis apply to a predominantly Caucasian population sample in a treatment setting whose average age is 74 years old. In this sample population, the impact of the mandatory sepsis protocol utilization on health outcomes was measured. While substantial improvements were noted in some areas, a decline or no differences were noted in others.

Mortality, the length of stay and health outcomes. The mortality rate unsurprisingly has consistently been higher in the older population in both groups, but an overall considerable improvement in the mortality rate was noted after the sepsis protocols were implemented. The duration of hospitalization for patients with sepsis, on average, was 0.7 days shorter. Although the improved mortality rate could have been anticipated with new protocols, a decline of health outcomes of sepsis survivors was noted in the post-implementation group. While LOS shortened after new guidelines were implemented, patients were discharged in a generally worse condition than those discharged prior to implementation. An increased number of patients who survived sepsis were unable to return to their prior living arrangements, were discharged to nursing facilities instead, or required additional help at home. Nevertheless, a substantial number of lives had possibly been saved, and the average length of hospital stay reduced.

Notably, among sepsis survivors, a considerably higher rate of readmission was recorded in the post-implementation group.

Utilization of antibiotics and the protocol. There was no noteworthy difference in antibiotic prescribing behaviors despite the fact that the post-implementation group's average duration of hospitalization was shorter, and there were fewer patients in septic shock. Whereas a higher percentage of patients had blood samples collected for lactic acid on time, unexpectedly fewer patients received timely initial antibiotics, and considerably fewer patients received AAT after the new Sepsis Bundle was initiated. The blood culture collection times and wait time for blood culture results were not affected by the bundles.

Other secondary findings. While a decrease in MDR infections was noted, a major increase in healthcare acquired infections was seen, which occurred in the context of a higher readmission rate, with pneumonia being a leading cause for both readmissions and healthcare acquired infections. An expected change in mental status often associated with sepsis was noted in a higher percentage among older patients in both groups. Finally, the results show a negligible relationship between age and LOS, a weak correlation between patients' outcomes at discharge and age, and a weak correlation between LOS and outcomes at discharge, but a strong relationship between LOS and the number of antibiotics prescribed.

The following chapter presents the discussion of findings outlined in this section, and implications of these findings for nursing practice, research, and policy.

CHAPTER V

DISCUSSION

Sepsis is a serious and often fatal condition affecting millions of people nationally and across the globe, and despite advances in medicine and technology, the outcomes of patients affected with sepsis remain poor. Patient outcomes not only depend on targeting the pathogen but on controlling the host response and reducing collateral organ and tissue damage.

The incidence of sepsis has been increasing over past decades, primarily as a result of an aging population and a milieu of antimicrobial resistance and growing numbers of drug-resistant pathogens. Wider use of immunosuppressive therapies, more accessible medical technology and interventions, and improved recognition of sepsis are other factors contributing to increased incidence and diagnosis of sepsis. Sepsis guidelines have been evolving with changing recommendations derived from emerging trials and evidence-based research. Efforts by healthcare organizations, government officials, and researchers to improve sepsis outcomes have been put forth in attempts to improve short-term and long-term survival. While there is a general consensus that the optimal approach to sepsis management is early recognition and rapid interventions, the methods of initial resuscitation and hemodynamic monitoring remain controversial.

This evidence-based project's focus was to evaluate the effectiveness of the newest sepsis protocol on patients' health outcomes and compare mortality, morbidity,

LOS, antibiotic utilization, and readmission rates before and after the protocol implementation in a community hospital in the coastal region of South Carolina. In addition, this project's goal was to assess whether implementing the mandated protocol actually influenced the timing of initiating early interventions. The protocol is a mandatory quality improvement measure known as the Sepsis Early Management Bundle (SEP-1) that went into effect on October 1, 2015, to monitor the quality of sepsis care in hospitals nationwide. The Sepsis Bundle is enforced by Medicare and adherence is measured by the timeliness of interventions.

A retrospective data analysis was performed that included 158 patients' medical records and compared patients' outcome before and after implementation of the sepsis protocols. The results presented in this paper apply to a population sample whose average age is 74 years, predominantly Caucasian, and hospitalized with sepsis in the setting noted above. In this sample population, the impact of mandatory sepsis protocol utilization on health outcomes was measured.

The expectations for this project's results were that outcomes of all aspects of sepsis care would improve with the use of the new sepsis protocols, including hospital length of stay (LOS) mortality, morbidity, and readmissions. Additionally, it was anticipated that having introduced the mandated protocol for timely carrying out specific therapeutic approaches to sepsis management would improve the timeliness to initiation of these interventions. The outcomes of this project showed that uniform improvement was not achieved. Given the results of this project, it can be assumed that the guidelines have made an impact on some aspects of sepsis management and care and outcomes but not others.

Evaluation of Findings

While results of this project do not necessarily infer causality, since the new protocol was made mandatory, considerably decreased mortality and reduced LOS were reflected in the post-implementation group as compared to the pre-implementation group. However, overall patients' outcomes, including long-term morbidity such as a functional status at the time of discharge and readmissions rates had worsened. Increased sepsis survival rates and shorter hospital stay after implementation of the sepsis protocol may, in fact, have contributed to these phenomena, because patients who would have otherwise died did survive, but did so with multiple negative health consequences.

Results of this project are consistent with evidence in literature (Delaney et al., 2013; Mouncey et al., 2015; Yealy et al., 2014) in which no significant decrease in sepsis morbidity or mortality was demonstrated when patients were treated with a strict protocol-based resuscitation strategy over individualized care at the discretion of the treating physician. Results showed a marked improvement in mortality, but overall worse health outcomes of those who survived sepsis.

Mortality. Major findings of this project included a considerably increased overall incidence of sepsis and septic shock survival rates after the new sepsis protocol was implemented. In reviewed literature, one study since Rivers et al. (2001) EGDT trial, showed a marked reduction of mortality (Chelkeba, 2015). This project showed a 20 % decrease in mortality rates after the Sepsis Bundle protocol was in place (41% mortality in the pre-implementation group and 21% in the post-implementation group). Proportionally 10% fewer patients went into a septic shock and were critically ill, but 16% more severe sepsis cases were recognized in the post-implementation group

compared to the pre-implementation group. These findings can be attributed to the EMR alert module and mandated measures. A substantial 28% decrease in the number of patients who were treated in the ICU, intubated and on a ventilator requiring respiratory support were recorded in the second group. It can be speculated that faster recognition of sepsis by providers may have improved the mortality outcome by preventing more patients from progressing to septic shock and death. Aside from the availability of more sophisticated treatments, the software generated sepsis alert, and the mandated measures, the potential explanation for the decreased mortality rate seen in this project's outcomes, which is supported by the literature, may be multifactorial (Vincent et al., 2013). Uniformly increased incidence of sepsis observed nationwide might be attributed to increased awareness of sepsis, but also overdiagnosis. Outcomes of this project show that after implementation of the new sepsis protocols in the community hospital, mortality rates were reduced and LOS shortened.

The length of stay. There are conflicting results in the literature that include questionable benefits of components of EGDT on LOS (Zhang et al., 2015); however, this project's findings did not reflect it. The average LOS for patients in this project decreased by a 0.7 day from pre-implementation to post-implementation time. Although the 0.7-day reduction in hospital LOS seems trivial, it is substantial for quality and cost-effectiveness of care. Such a difference can contribute to lower patients' exposure to iatrogenic complications. Furthermore, given the estimated costs associated with a day in the hospital, a 0.7-day reduction would translate into approximately $1,500 in savings for every inpatient admission (Gryczynski et al., 2016).

These findings can be associated with more efficient resource utilization and cost-effectiveness of sepsis care. This is likely to be attributed to improved sepsis awareness, earlier recognition, and prompt treatment. Interestingly, on average, patients in the post-implementation group were 4.7 years older and, hypothetically, the final results might show greater improvement if adjusted for age. These findings alone are optimistic and encouraging, and if accurately owed to the protocol and enduring, they will likely contribute to substantial cost savings on the utilization of healthcare resources. However, while mortality and LOS were substantially lower in the post-implementation group, the health outcomes of survivors were generally worse.

Morbidity. Although more patients survived sepsis, they often lost their independence and required long-term care or assistance at home. A large percentage of sepsis survivors were unable to return home and were discharged to rehabilitation nursing facilities. They were also more likely to be rehospitalized with recurrent infections. Older age and multiple comorbidities, disabling consequences of sepsis, as well as possible premature discharges (shorter LOS) may be attributed to sepsis survivors' poorer health at the time of discharge preventing them from returning to their previous functional status.

Sepsis has been associated with the development of at least one new physical limitation for survivors and with a 3-fold risk of developing moderate to severe cognitive impairment (Iwashyna et al., 2010). Sepsis survivors report deterioration in the quality of life related to poor physical function and overall declined health (Turi & Ah, 2013). In regards to morbidity, this project's finding is consistent with the evidence in the literature (Turi & Ah, 2013; Wang et al., 2014). Among patients in the post-implementation group,

treated for sepsis after protocols were put in place, as many as 64% of those who survived were discharged in lower functional status than prior to hospitalization, as compared to a 38% in the pre-implementation group. Overall, this accounts for a 26% difference. The decreased functional status in the second group appears to be explainable by higher survival rates. While mortality in the same group was reduced by 20%, the survivors were likely left with more severe comorbidities as a result of sepsis.

Interestingly, among the sepsis survivors in the post-implementation group whose functional status was worse at the time of discharge as compared to their functional status prior to admission, were on average 17 years older from those in the same group but whose status did not change. There was an average 14 years difference in age between those patients with worse outcomes at the time of discharge in the post-implementation group than in the pre-implementation group was 14 years. Age seems to be playing an important role not only in the incidence and mortality but also in the sepsis morbidity. Evidence in literature also shows that older age is an independent predictor of poor outcomes of sepsis (Martinal, 2006). Persons older than 65 years of age with multiple comorbidities are at a higher risk for complications from infections than the general population. Therefore, since worse outcomes in the post-implementation group could be explained by the higher survival rates as well as the overall older age, in the future, it could be useful to adjust for these differences in evaluating outcomes.

Only 21% of patients in the post-implementation group were discharged to prior living arrangements compared to 23% in the pre-implementation group. Patients in the post-implementation group were more frequently discharged to nursing facilities (19% in contrast to 12% in the pre-implementation group), and considerably more frequently

required home health or higher level of care (32% in contrast to 20% in the pre-implementation group). These patients were at higher risk of developing recurrent infections and further complications and were consequently more prone to rehospitalizations.

Readmissions. Hospitals are paid by Medicare, Medicaid and third party payers based on a formula that is specific to categories of diagnoses referred to as Diagnosis Related Groups (DRG's) (Case Management Innovations, 2016). The payments for the DRGs are predetermined, and the amount does not change regardless of the cost of care. Hospitals make profits by providing medically appropriate care and discharging patients in a timely manner, but at the same time keeping the costs below the amount of the DRG payment. If the cost exceeds the payment, then the hospital will lose money in that case (Case Management Innovations, 2016). Early discharges may be driven by high costs of acute care hospitalization, especially in intensive care units, and diagnosis- related recommended average LOS. This project demonstrated disproportionally higher (47%) readmission rates in the post-implementation group as compared to the pre-implementation group (17%). This finding could be explained by patients being discharged too soon in an effort to control costs based on DRGs as indicated by the finding of a 9% reduction in LOS following implementation of protocols.

Readmission rates among sepsis survivors increased substantially in the period measured after implementation of the sepsis protocol, from 17% to 47%. High readmission rates are also documented in the literature. A retrospective cohort study of adults hospitalized with severe sepsis showed that 26% of severe sepsis survivors were readmitted within 30 days of discharge, 48% were readmitted within 180 days, and the

mean cost of each readmission was $25,505 (Goodwin, Rice, Simpson, & Ford, 2015). In this project, of the 34 of the 72 patients with sepsis in the post-implementation group were readmitted. These high readmission rates can lead to significant health care expenditures. Based on the average cost of readmissions, an estimated cost for readmissions in this setting could reach $870,000 including only those rehospitalized patients from the post-implementation group, as compared to an estimated $380,000 prior to the protocols being in place. It should be taken into consideration, however, that the sepsis survivors in the second group were on average 4.7 years older and generally in poorer health.

Patients presenting with sepsis often are also burdened with multiple comorbidities that may contribute to readmissions. Under the Hospital Readmissions Reduction Program (HRRP), hospitals with excess readmissions for selected common diagnoses such as heart failure, myocardial infarction, pneumonia, chronic obstructive lung disease, and total hip or knee procedures are penalized up to 3% of all Diagnosis-Related Group payments (Adamson, Bharmi, Dalal, & Abraham, 2015). Severe sepsis readmission places a substantial burden on the healthcare system, with one in 15 and one in five severe sepsis discharges readmitted within 7 and 30 days, respectively (Donnelly, Hohmann, & Wang, 2015). Hospitals pay a high price in penalties for readmissions. Hospitals and clinicians should be aware of this important sequela of severe sepsis (Donnelly, Hohmann, & Wang, 2015).

Impact on protocol utilization. Uniform improvement in utilization of the elements of the sepsis protocol and timeliness in initiating treatments were expected since the Sepsis Bundle protocol became mandatory, especially in the context of associated

preceding staff education and EMR updates to include sepsis alerts and prompts for protocol exploitation. However, in this particular hospital, implementation of mandatory sepsis protocols did not improve intervention processes when the interventions were bundled together. While individual elements of the bundle, such as drawing lactic acid, improved (on average, the first lactic acid sample collection within three hours of presentation improved 17%, and obtaining repeat lactate within six hours improved 38%), unfortunately the timeliness of initiating antibiotics and the appropriateness of antimicrobial agent choice substantially deteriorated. Moreover, with the new protocol in place, 49% of qualifying patients had the second lactic acid collected, which is a major improvement from 11% in the pre-implementation group, but still short of meeting standard protocol. Initiation of appropriate IV fluids improved 7% in the post-implementation group, and there was no difference (80% for both groups) between groups in drawing blood samples for cultures within three hours and prior to initiation of antibiotics.

No clear explanation for these phenomena or associations with other variables could be established based on the results of data analysis in this project. This protocol is positively influencing some aspects of sepsis care that could continue to improve with consistent use, but did not have much of an impact on the other aspects, such as the antibiotics utilization warranting the necessity for continued attention to this issue. Potentially, if better antibiotic utilization was possible in combination with the protocol, improvements in both mortality and morbidity could be achieved.

Appropriateness of antibiotics utilization. No significant change was seen in timeliness of obtaining blood cultures before and after implementation of protocols,

therefore there was no difference in the time until pathogens were identified. No change in the current long waiting time for the culture results was anticipated since this is dependent on the hospital microbiology techniques and currently available technology, not on the new protocols. A long waiting time for cultures results in a greater period of time that empiric, broad-spectrum antibiotics are utilized. Moreover, the necessity to treat unidentified pathogens probably contributes to inappropriate antibiotic choices, which in turn encourages breeding resistant microbes and leads to an increase in multi-drug resistant organisms. The proportion of patients receiving AAT within the first three hours of sepsis onset decreased from 72% in the pre-implementation group to 58% in the post-implementation group. Nearly 60% of patients in the post-implementation group received inappropriate antibiotics based on subsequent cultures results.

This problem occurs similarly in this facility and across the nation in facilities that still use traditional methods to obtaining blood cultures results. Current standard blood culture procedures consist of inoculating blood cultures bottles and monitoring for the growth of microorganisms. Cultures are allowed to grow for 24 to 72 hours or longer, with subsequent subcultures and susceptibility to antibiotics testing results (Dekmezian, Beal, Damashek, Benavides, & Dhiman, 2015). This process creates a considerable delay in initiating AAT from the initial collection of blood sample from the patient to delivery of the most appropriate antimicrobial treatment. Newer technologies such as molecular diagnostics offer rapid identification and might be more efficient diagnostic tool for the treatment of infections.

Additional Findings

The most common source of infection among adults is the lung or lungs, and pneumonia is the leading cause of sepsis nationwide. While community-acquired pneumonia is the most frequently seen cause of sepsis, pneumonia can also be caused by a healthcare-associated infection that affects 1.7 million hospitalizations in the United States every year (Sepsis Alliance, 2016). In this setting, the incidence of pneumonia in septic patients accounted for 50% of all sepsis causes in both groups, followed by urinary tract infections. While a trivial decline in the incidence of MDR infection was recorded in the post-implementation group, there was a major increase in nosocomial infections, from 13% in the pre-implementation group to 36% in the post-implementation group. Pneumonia was seen as the most frequent reason for readmissions (56% in the post-implementation group, compared to 15% in pre-implementation group), and 47% of those readmitted cases in the post-implementation group were associated with healthcare-acquired pneumonia compared to 13% in the pre-implementation group. Furthermore, of all deceased patients in both the pre-intervention and post -intervention groups, over 70% had a diagnosis of sepsis related to pneumonia. These findings may be associated with increased survival rate but a poorer health status of survivors. As more people survive sepsis, survivors are frequently struggling with serious health issues and they are prone to recurrent infections including pneumonia and sepsis.

Another noteworthy unexpected finding was that 76% of septic patients also experienced a mental status change and those patients were on average 9.8 years older than those who did not experience acute mental status change associated with sepsis. This finding may be important in diagnosing sepsis in elderly patients. In addition, there

was an association found between the number of empiric antibiotics prescribed and the LOS. While the results cannot demonstrate causality, an assumption can be made that sicker patients did not respond to treatments as expected. This is likely due to their more severe presentation, multiple comorbidities or immunocompromised status, thus the necessity to use a greater number of broad-spectrum antibiotics and longer hospitalization.

Limitations

One of the limitations of this study was that the overall sample size was small. This project involved patients with a mean age of 74. In addition, patients in Labor and Delivery, Gynecology, Neonatal, and Pediatric wards were not included in this study, which could have influenced the results consequently yield different results as these individuals are very likely different from the participants chosen for this project.

Post-implementation group participants were on average 4.7 years older which should be taken into consideration when comparing both groups. Other confounding variables such as comorbidities may have also affected patients' outcomes. Since comorbidities were not included in the analysis, it is important to acknowledge that certain aspects of the participants' health history may have affected the outcomes.

With objectivity in data collection, potential measuring bias is low. The access to the data in a retrospective review reduces the possibility of data collection, calculation or transcription errors. Reliability can be established with accuracy of the tools used for data analysis that produces stable and consistent results, and validity with concepts accurately measured, although clinicians' judgments and charting error cannot be completely excluded.

Recommendations

Recommendations for Practice. Results of this project suggest the need for improvement and innovative approaches to therapeutic and diagnostic methods that could facilitate earlier and more targeted interventions in this acute care hospital setting. Methods such as an antimicrobial stewardship program and rapid diagnostic technology can generate a better response to treatment, and potentially improve sepsis outcomes, save resources, and help to reduce MDR organisms. Utilization of antimicrobial stewardship programs in inpatient settings has many benefits including improved patient outcomes, reduced adverse events such as *Clostridium difficile* infection, improvement in rates of antibiotic susceptibilities to targeted antibiotics, and optimization of resource utilization across the continuum of care (Calderwood et al., 2015). Antibiotic stewardship programs are designed to implement guidelines and strategies to reduce antibiotic therapy to the shortest effective duration and increase both appropriate uses of oral antibiotics and the timely transition of patients from empiric to narrow spectrum targeted treatment. The rising threat of antimicrobial resistance calls for rapid interventions with appropriate antimicrobial choices in sepsis treatment.

In this setting, an interdisciplinary team dedicated to improving sepsis outcomes has been functioning, but a more robust, dedicated antimicrobial stewardship program would be beneficial in sepsis treatment as well as in attempts to combat antibiotic resistance, reinfections, and superinfections. This stewardship program should be formed by a multidisciplinary team consisting of practicing clinicians, such as a hospitalist physician or a nurse practitioner, in collaboration with clinical pharmacists, clinical microbiology staff, the infectious disease specialist and the infection control staff. The

team should implement local strategies aimed at timely delivery of appropriate antibiotic therapy and timely de-escalation of empiric antimicrobials to narrower spectrum agents to improve outcomes and reduce the length of stay (Zhang Micek & Kollef, 2015). Local strategies include collaboration between prescribers, pharmacists, and the entire team, and knowledge of antimicrobial susceptibilities of local bacterial isolates and resistance patterns to aid inappropriate empiric antibiotic selection. The team should focus on prompt de-escalation of antibiotics based on cultures and sensitivities, and continue to explore innovative diagnostic technologies to allow earlier identification of pathogens.

Rapid diagnostic testing in addition to conventional cultures combined with active antimicrobial stewardship program support has the potential for considerable improvement of sepsis management and patients' outcomes (Barlam et al., 2016). Advantages to transition to rapid diagnostic technology such as molecular diagnostics would far outweigh any disadvantages including cost because this technology has the potential to have readily available, objective, and reproducible tests that guide specific treatment of infections (Wilson, 2015). This project's findings have to be integrated with collaborative sepsis team efforts to improve sepsis outcomes in this setting, and use data to validate best practice recommendation.

Not all sepsis is created equal and a cookie cutter approach should not be used in the treatment approach. Sepsis does not follow any algorithm and does not always progress in a predicted direction. It is a misconception that sepsis always progresses gradually from sepsis to severe sepsis to septic shock; therefore, applying treatment templates would not always yield desired results. There are no specific thresholds to sepsis, and applying standard measures to such a complex and rapidly progressing

condition is likely to fail in achieving uniform improvement in outcomes. Enforcing obligatory standardized measures as templates to combat sepsis proved unsuccessful in many aspects of health outcomes, as shown in this project's results and supported by the evidence-based literature. Therefore, applying individualized clinical judgments to treatments such as aggressive fluid resuscitation and empiric antibiotic use, utilization of knowledge of individual patient's history and local antibiogram make-up, in addition to evidence-based guidelines and protocols could result in the most favorable outcomes.

Recommendation for Future Research. Healthcare providers should anticipate seeing more sepsis cases in the future, partially as a result of better recognition of the condition, but primarily because people are now living longer with multiple comorbidities that are currently treatable. Future studies are needed to identify approaches that can help the increasing older population of sepsis survivors to regain independence, return to prior living arrangements, and avoid rehospitalizations. Again, a possible assumption can be drawn that a relationship exists between the rate of patients experiencing worse outcomes and readmissions. Further analysis to estimate these associations and an intervention research related to discharge planning and prevention of readmissions would be beneficial to approaches to sepsis care.

Whereas early diagnosis of sepsis and prompt initiation of antibiotic treatment improve survival, methods of initial resuscitation and hemodynamic monitoring remain controversial. The nuances of aggressive fluid administration to all septic patients, and using vasopressors in early septic shock are divisive and not completely defined; therefore, more research is needed to further validate the most practical methods for optimal sepsis treatment. Further investigation would also be beneficial to establish

direct evidence regarding safety and efficacy of early de-escalation of antimicrobial agents for adults with sepsis, severe sepsis or septic shock (Silva, Andriolo, Atallah, & Salomão, 2013).

Sepsis in the elderly population is a common problem associated with considerable mortality and major consumption of healthcare resources. These findings have implications for resource prioritization and provide insights for expanded scientific investigation (Martin et al., 2006). A separate study utilizing sepsis data would be useful to evaluate sepsis outcomes given advanced age and pre-existing conditions. In addition, a study researching altered mental status in elderly patients as a sign of impending sepsis would be helpful for healthcare providers in recognizing sepsis in this vulnerable population. Since pneumonia was the leading cause of sepsis and death from sepsis, it could be beneficial to further investigate this problem, including for example investigation of pneumonia occurrences, preventative measures, and vaccination rates.

Despite extensive research, advances in medicine and technology, knowledge of sepsis pathophysiology and complexity of its mechanisms is still limited, and finding optimal sepsis management strategies is challenging. More research is needed addressing best evidence practice, as currently available therapies do not provide a cure. Future study on more individualized approaches for better therapeutic response is needed (Iskander, et al., 2013).

Recommendation for Policy. Given the limitations to current guidelines as outlined in this project, recommendation for the general policy is to consider updating sepsis definitions; specifically, clarifying SIRS and severe sepsis definitions before mandating sepsis measures. Today, diagnosis of sepsis relies on nonspecific

physiological criteria and causative microorganism detection based on culture assays. This results in diagnosis and treatment delays, and improper use of antibiotics. Since symptoms of sepsis can be vague especially in its early stage, it is difficult, if not impossible to denote the exact time of initial sepsis onset, which is an important point of reference in current treatment guidelines and a marker for quality measures. This may lead to inappropriate prescribing of antibiotics in order to comply with the measure.

The key to effective treatment of sepsis is fast detection and rapid initiation of treatment. Recommendations for policy improvement for this hospital include consideration to establishing a Code Sepsis call in addition to current sepsis guidelines, and a medical sepsis team dedicated to the rapid recognition and timely initiation of appropriate treatments. Ongoing staff education is fundamental because tight coordination and communication are needed among the entire team. The risk of having Code Sepsis is that the code can inadvertently be called to patients who do not have sepsis but meet severe sepsis criteria, and unintentionally captured by the sepsis measure matrix. Consequently, this raises concerns about antibiotic overuse. Therefore, other than simply accepting the risk, it is imperative to have a policy in place regarding appropriate antibiotic use and de-escalation once deemed safe for patients and coordinated by designated antimicrobial stewardship program team.

Despite an emphasis on the appropriateness of antibiotic administration, measuring effects of antibiotics' appropriateness and effectiveness against pathogens is only possible with known culture and sensitivity data, is not usually available for 24 to 96 hours (Puskarich et al., 2011). Therefore, the antimicrobial stewardship team needs to be focused on providing evidence to influence the hospital administration to consider

investing in the innovative diagnostic technology to allow earlier identification of pathogens and, in the spirit of antimicrobial stewardship, better-targeted antibiotic treatment.

Hospital administration should also consider assessing discharge practices to evaluate for potential premature discharges. While each additional day of hospital stay over the recommended LOS based on DRG is not cost effective as it falls outside of the bundle payments for the hospital, readmissions can be much more expensive and premature discharges can have serious negative health consequences for patients.

Based on results of this project, drawing the second lactic acid was especially deficient in both the pre- and post-implementation measures. Therefore, another recommended innovation, in order to improve compliance with sepsis guidelines, includes building into the existing sepsis power plan in the EMR software an additional automated reflux order prompting providers to repeat a lactic acid level for qualified patients.

Standardizing sepsis care proves to be challenging. Proportionally more diagnoses of severe sepsis were made after the protocol went into effect. This could be attributed to overdiagnosis based on the protocol's controversial criteria for SIRS and severe sepsis. The concepts of SIRS and severe sepsis with their low specificity and high sensitivity can lead to misinterpretations and discrepancies in reported incidence and observed mortality. Therefore, data collected retrospectively for the quality measure could inadvertently include patients that were perhaps not septic at all, thus incorrectly showing more survivors among patients labeled with severe sepsis. Hospitals not treating these patients accordingly as per the protocol can trigger a quality measure deficit based

on the mandatory quality improvement measure known as the Sepsis Early Management Bundle (SEP-1). Hospitals will likely be struggling with this measure; therefore, the severe sepsis definition should be clarified for the purpose of the accuracy of data collection for quality measures. In the case of severe sepsis (SIRS with infection and evidence of organ damage), it should be made clear that the organ dysfunction is a new condition related to current infection, and quality procedures should leave room for individual clinical judgment. Measures of sepsis guideline effectiveness should focus on not only immediate results and improved mortality rates, but also long-term debilitating effects affecting survivors. Both short-term survival and long-term morbidity, including a return to function, should be considered as important outcomes.

Conclusions

This report summarizes the retrospective review of effects of sepsis protocols on health outcomes, particularly mortality, hospital LOS, morbidity, readmissions, antibiotics utilization, and the protocol's impact on the early initiation of treatment in a South Carolina community hospital. This project showed that implementation of mandatory sepsis protocols did not uniformly improve intervention processes. Moreover, results did not clearly demonstrate that the Sepsis Bundle interventions improved overall outcomes. The mortality and LOS improved, but health outcomes of survivors did not. While the utilitarian goal to reduce mortality is reasonable, the increasing numbers of sepsis survivors are at high risk for worse long-term negative health outcomes. These patients may be discharged into nursing facilities from the hospital prematurely and in worse functional status and health than prior to hospitalization. This puts them at risk for

remaining in long-term care homes and prone to readmissions because of the debilitating nature of sepsis.

This project is an exploration of a PICO question that addresses a current problem with sepsis management in the South Carolina's community hospital, which is relevant to DNP practice. The methodology described above is an attempt to determine the impact of the newest Sepsis Management Bundle on patient outcomes and feasibility to recommend practice change in this facility. Sepsis is common in hospitals and its outcomes are frequently fatal. Prompt recognition and effective treatment are serious issues that this and other hospitals are facing across the nation. This project offers the stakeholders an educational opportunity to gain new knowledge regarding the severity of the problem of sepsis and its management among inpatient adults in this hospital, and the effects of the current sepsis protocol on patients' outcomes.

Evidence in the literature supports the conclusion that enforcing protocols alone is unlikely to bring anticipated results. An open-minded approach is needed to sepsis interventions, with criteria and guidelines that allow room for clinical judgment. Sepsis guidelines should focus not only on survival but also on long-term consequences for survivors and their return to their prior level of functioning. Administration of appropriate antibiotics may be the single most important factor in reducing both long- and short-term morbidity and mortality from sepsis (Marik, 2014). Antibiotic treatment efficiency can be best achieved with robust antibiotic stewardship programs and can be improved with rapid diagnostic technology. Nevertheless, no single sepsis-specific treatments exist and core management of patients still relies mainly on early recognition, initiation of treatment, and source control. Accurate and prompt diagnosis of sepsis,

identification of causative pathogens, and initiation of appropriate antibiotic treatment are paramount approaches to sepsis, but the protocol's interventions remain a source of controversy, and timely recognition remains a challenge for healthcare professionals. Although the Sepsis Bundles have already been enforced by CMS, new clinical trials are needed to update sepsis criteria and definitions, to evaluate the effect of interventions on short and long-term health outcomes and determine best evidence-based approaches.

As the knowledge of sepsis pathobiology improves and technology continues to advance, the recommendations for sepsis treatment will continue to evolve and change based on emerging new evidence as they have over past decades (Lopez-Bushnell, Demaray, & Jaco, 2014). This quality improvement project might serve an introductory work in developing a research study that can be generalizable to other settings and more globally address the challenge of sepsis management.

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APPENDIX A: EVIDENCE TABLE

Table A.1. *Evidence Table*

Brief Reference	Type of Study/ Quality Rating	Methods	Threats to Validity/ Reliability	Findings	Conclusions
Angus, D. C., Barnato, A. E., Bell, D., Bellomo, R., Chong, C. R., Coats, T. J., ... & Howe, B. (2015).	Systematic review and meta-analysis of RCT IA	Meta-analysis of RCTs published from January 2000 to January 2015; (n=4735 patients) sought to determine whether EGDT compared with usual care reduces mortality for ED patients with septic shock	All RCT scored high except for lack of blinding	EGDT is not superior to usual care for ED patients with septic shock, no effect in primary and 90-day mortality	EGDT for patients presenting to ED with early septic shock does not decrease mortality but increases ICU resources utilization.
Banerjee, R., Teng, C. B., Cunningham, S. A., Ihde, S. M., Steckelberg, J. M., Moriarty, J. P., ... & Patel, R. (2015).	Prospective randomized controlled trial IA	A total of 617 patients with positive blood cultures were included, randomized to three groups: control, n = 207, rmPCR n = 198 and rmPCR/AS, n = 212.	Relatively small sample, otherwise none identified	Intervention group had shorter time to microbe ID (1.3 hr) vs. control (22.3 hr) ($P < .001$) and decreased broad-spectrum antibiotic use (control 56 hr, rmPCR 44 hrs, rmPCR/AS 45 hr; $P = .01$) and increased narrow-spectrum (control 42 hr, rmPCR 71 hr, rmPCR/AS 85 hr; $P = .04$) use, control 24 hours, rmPCR 6 hours, $P = .04$).	Groups did not differ in mortality, LOS, or cost. rmPCR reduced use of broad-spectrum antimicrobials. Addition of antimicrobial stewardship enhanced antimicrobial de-escalation.

Chelkeba, L., Ahmadi, A., Abdollahi, M., Najafi, A., & Mojtahedzadeh, M. (2015).	Systematic review and meta-analysis of RCT IA	Trial included RCTs, total of nine trails comprising 4783 patients that compared EGDT with usual care	Six studies low risk of bias, remaining studies unknown risk of bias. None of the these included nine trials were double blinded as it is difficult to blind the clinicians in such difficult situations, and we believe that such act did not influence the outcomes of interest.	The study found that EGDT significantly reduced mortality in a random-effect model (P = 0.008); significantly reduced mortality in low to middle economic income (P = 0.002) compared to those in higher income countries (P = 0.28).On the other hand, patients receiving EGDT had longer length of hospital stay compared to the usual care (P = 0.07);	The result of our study showed that EGDT reduced mortality in patients with severe sepsis and septic shock. Paradoxically, EGDT increased the length of hospital stay compared to usual routine care.
Delaney, A. P., Peake, S. L., Bellomo, R., Cameron, P., Holdgate, A., Howe, B., ... & Webb, D. (2013).	ARISE (Australasian Resuscitation in Sepsis Evaluation) multicenter prospective, randomized trial IA	Designed to test the EGDT hypothesis as compared to usual care, this trial was conducted at 51 tertiary care and non-tertiary care metropolitan and rural hospitals across Australia and New Zealand. 796 patients were assigned to the EGDT group and received care based on the original EGDT resuscitation algorithm, and 804 control patients received usual care at the discretion of the treating physician	Trial could not be blinded, but risk of bias minimized through central randomization	Study results demonstrated that patients in the EGDT group were more likely to receive vasopressor infusion, red-cell transfusion, and dobutamine infusion. However, despite an increased rate of aggressive therapy, there was no significant difference in 28- and 90-day mortality, hospital mortality, organ support and LOS between the two treatment groups	Adherence to the EGDT algorithm did not offer a survival advantage over usual care for patients presenting to the emergency department with early septic shock.

Jones, A. E., Shapiro, N. I., Trzeciak, S., Arnold, R. C., Claremont, H. A., Kline, J. A., &. (2010).	RCT, multicenter, prospective, randomized, non-blinded clinical trial IA	The study evaluated whether lactate clearance could be an equally effective measure of tissue oxygen delivery and an alternative to central venous oxygen saturation ($ScvO_2$) measurement. Included in data analysis were 294 patients, 147 patients were assigned to the control $ScvO_2$ group, and 147 to the lactate clearance group.	None identified	Study results demonstrated no difference in frequency of any treatments administered during the six-hour resuscitation period and throughout the initial 72 hours of hospitalization to maintain high compliance with the target goals (CVP, MAP, and $ScvO_2$, or lactate clearance)	Measurement of lactate clearance, a quicker and more non-invasive measurement, can be an equally effective alternative to $ScvO_2$ monitoring in goal-directed resuscitation.
Mouncey, P. R., Osborn, T. M., Power, G. S., Harrison, D. A., Sadique, M. Z., Grieve, R. D., ... & Rowan, K. M. (2015).	(ProMISe) Multicenter, pragmatic, open, parallel group randomized controlled trial with integrated economic evaluation IA	Trial conducted in 56 hospitals in England from February 16, 2011, to July 24, 2014, enrolled 1260 patients, 630 in EGDT group and 630 in usual care	Interventions could not be blinded, but the risk of bias minimized through central randomization. Since lower than anticipated death rate, this study outcome may not apply to settings with higher mortality	Mortality was 29.5% in EGDT group and 29.2% in the usual care, and no significant difference in any other outcomes including health-related quality of life, or rated in serious adverse events. Moreover, on average, EGDT was associated with increased costs.	EGDT strict protocol and addition of $SCVO_2$ monitoring did not lead to improvement in outcomes. Of note, decreasing mortality is a trend in recent years, and many aspects of sepsis care have evolved since Rivers et al. (2001) study 15 years ago.

Peake, S. L., Delaney, A., Bailey, M., Bellomo, R., Cameron, P. A., Cooper, D. J., …& Williams, P. (2014).	Prospective, randomized, parallel group trial IA	From October 5, 2008, to April 31, 2014, a trial was conducted in 51 tertiary and non-tertiary metropolitan and rural hospitals	Trial could not be blinded, but risk of bias minimized through central randomization	In critically ill patients presenting to the emergency department with early septic shock, EGDT did not reduce all-cause mortality at 90 days	The value of incorporating EGDT into international guidelines as a standard of care is questionable
Sterling, S. A., Miller, W. R., Pryor, J., Puskarich, M. A., & Jones, A. E. (2015).	Systematic review and meta-analysis; IA	11 included studies, 16,178 patients were evaluable for antibiotic administration timing from emergency department triage. The study sought to determine the association between timing of antibiotic administration and mortality in severe sepsis and septic shock.	None identified	Contrary to Kumar et al. (2006) study, this study found no increased mortality in the pooled odds ratios for each hourly delay from less than 1 to more than 5 hours in antibiotic administration from severe sepsis/shock recognition.	No significant mortality benefit of administering antibiotics within 3h of ED triage or within 1 hour of shock recognition in severe sepsis and septic shock. These results suggest that currently recommended timing metrics as measures of quality of care are not supported by the available evidence

Yealy, D. M., Kellum, J. A., Huang, D. T., Barnato, A. E., Weissfeld, L. A., Pike, F., ... & Angus, D. C. (2014)	ProCESS (Protocolized Care for Early Septic Shock) A prospective multicenter randomized trial IA	The study evaluated whether all aspects of the original EGDT protocol (by Rivers, 2001) were necessary. 31 academic EDs across the United States participated, in this study. 1,341 patients meeting criteria for severe sepsis and septic shock were included in data analysis; 439 patients received EGDT according to the original protocol, 456 control patients received standard care, and 446 patients received protocol-based standard therapy.	Generalization across various healthcare settings and outside of the United States is uncertain, more evidence is needed.	Despite more aggressive therapy in the protocol-based groups, there was no significant difference in 60- and 90-day mortality between the treatment groups; no significant differences in the incidence and duration of cardiovascular or respiratory failure, LOS, in sepsis morbidity or mortality when patients were treated with a strict protocol-based resuscitation strategy over usual care at the discretion of the treating provider	This study outlined a protocol for administration of fluid and vasoactive agents to reach goals for systolic blood pressure, shock index, and fluid status, without mandating invasive venous access, aggressive blood transfusion, and inotropic support. A combination of EGDT and protocol based therapy offers no survival benefits as compared to not-protocol-based usual care.

Zhang, L., Zhu, G., Han, L., & Fu, P. (2015).	Systematic review and meta-analysis of RCTs IA	10 RCTs included from 2001 to 2014 involving 4,157 patients	Among all RCTs, none of them were double-blinded. However, blinding of patients and clinicians was extremely difficult in these studies to evaluate a complex intervention such as EGDT protocol, and the authors judged that the primary outcome (mortality) is not likely to be influenced by lack of blinding	EGDT was associated with a higher mortality rate in comparison with the early lactate clearance group ($P = 0.02$). In the first 6h EGDT received more inotropic agents ($P = 0.04$), fluid administration ($P = 0.05$), and red cell transfusion ($P < 0.01$). There were no significant differences in length of ICU stay ($P = 0.73$) or in-hospital stay ($P = 0.57$), ventilation rate ($P = 0.53$), and vasopressor support ($P = 0.63$).	No significant difference in mortality between the EGDT and the control group
Gu, W. J., Wang, F., Bakker, J., Tang, L., & Liu, J. C. (2014).	Meta-analysis of RCTs IB	13 trials involving 2,525 adult patients were included.	Strong and definitive recommendations cannot be made given variable quality of the studies .	GDT significantly reduced overall mortality in the random-effects model (P=0.01); mortality benefit was seen only in the subgroup of early GDT within the first 6 hours	The results of the present meta-analysis suggest that GDT reduces overall mortality in patients with sepsis, especially when initiated early.

Puskarich, M. A., Trzeciak, S., Shapiro, N. I., Arnold, R. C., Horton, J. M., Studnek, J. R., ... & Jones, A. E. (2011).	Pre-planned analysis of a multicenter prospective, parallel group, randomized controlled trial of early sepsis resuscitation IB	Study was designed to assess the non-inferiority of lactate clearance versus central venous oxygen saturation, evaluated adult septic patients in 3 urban EDs in the United States	Non-blinded. Only able to draw conclusions regarding associations and not causation.	The study found no increase in mortality with each hour delay to the administration of antibiotics after triage. However, delay in antibiotics until after shock recognition was associated with increased mortality.	Among patients who received antibiotics after shock recognition, mortality did not change with hourly delays in antibiotic administration
Xu, J., Yang, Y., & Qiu, H. (2016).	Meta-analysis of RCTs IB	Nine studies compared EGDT with control care, and 5202 severe sepsis and septic shock patients were included.	More powered, randomized controlled trials are needed to determine the effects	A non-significant trend toward reduction in the longest all-cause mortality was observed in the EGDT group compared with control care	Trial sequential analysis indicated lack of firm evidence for a beneficial effect of EGDT

Yu, H., Chi, D., Wang, S., & Liu, B. (2016).	Meta-analysis of RCTs IB	5 studies enrolled 4303 patients with 2144 in the EGDT group and 2159 in the control group. The trial was conducted to determine whether patients with severe sepsis or septic shock could benefit from the EGDT protocol recommended by SSC Guidelines.	Included trials are not sufficiently homogeneous and potential confounding factors in the negative trials (ProCESS, ARISE, and ProMISe) might bias the results and diminish the treatment effect of EGDT	Overall, there were slight decreases in mortality within 28 days, 60 days and 90 days in the random-effect model in patients with severe sepsis or septic shock receiving EGDT resuscitation. However, none of the differences reached statistical significance	Data from five RCTs and found no survival benefit of EGDT in patients with sepsis. Further well-designed studies should eliminate all potential source of bias to determine if EGDT has a mortality benefit.
Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, & Peterson E. (2001).	Single –center, prospective, randomized trial IC	The study included 263 patients who met criteria for severe sepsis and septic shock; 130 subjects received EGDT and 130 controls received standard care. Study examined the effects of Early Goal Directed Therapy (EGDT) to evaluate the efficacy of the therapy prior to admission to Intensive Care Unit (ICU)	Small sample, external validity threat due to single center study. Potential bias resulting from the direct influence of the investigators on the care of the patients in the treatment group	In-hospital mortality was 30.5% in the group assigned to EGDT, compared to 46.5% in the standard therapy group in short-term treatment (p=0.009). Mortality was 33.3% in EGDT group (p=0.01) compared to and 49.2% in control group in 28 day mortality rate , and 44.4% EGDT group (p=0.03) to 56.9% standard therapy groups in 60-day long-term mortality outcomes	This landmark article demonstrated both long and short-term mortality benefit when EGD was introduced within the earliest possible stages of sepsis while patients are still in ED and prior to going to ICU.

Jones, A. E., Brown, M. D., Trzeciak, S., Shapiro, N. I., Garrett, J. S., Heffner, A. C., & Kline, J. A. (2008).	Systematic review and meta-analysis of RCT IIB	The study sought to measure the treatment effect of quantitative resuscitation on mortality from sepsis. Nine RTCs were included and total sample of 1001 subjects	No blinding, limitations of making inferences based on between-study rather than within-study comparisons. Potential bias due to its retrospective approach, and possibility of unreported cointerventions influenced results	The study demonstrated a survival benefit afforded by quantitative resuscitation to treat sepsis at or near the time of recognition. There is lost if the intervention is initiated late. Study demonstrated support for the Surviving Sepsis Campaign recommendation	Applying an early quantitative resuscitation strategy to patients with sepsis imparts reduction in mortality.
Dettmer, M., Holthaus, C. V., & Fuller, B. M. (2015)*.	Retrospective observational cohort study IIIB	Multivariable model was used in this study of 243 adult patients with severe sepsis and septic shock to assess outcome differences between the serial lactate and no serial lactate cohorts to assess clinical outcomes	Small sample. This is a retrospective study which limits causal inference	Lack of serial lactate monitoring was independently associated with mortality. Serial lactate monitoring is associated with an increase in crystalloid administration, resuscitation interventions, and improved clinical outcomes in ED patients with severe sepsis and septic shock	Study results suggest that serial lactate monitoring, targeting a reduction in lactate levels to normal, is a generalizable resuscitation target in the ED.

Marik, P., & Bellomo, R. (2015).	Retrospective study IIIB	Article reviews the haemodynamic changes associated with sepsis and provides an approach to fluid management		Sepsis is primarily not a volume-depleted state and most septic patients are poorly responsive to fluids that are sequestered in the tissues, resulting in severe edema. A physiologic, haemodynamically guided conservative approach to fluid therapy is prudent, would likely reduce the morbidity and improve the outcome	Aggressive IV fluid resuscitation does not improve the outcome of patients with severe sepsis and septic shock
Waechter, J., Kumar, A., Lapinsky, S. E., Marshall, J., Dodek, P., Arabi, Y., ... & Cooperative Antimicrobial Therapy of Septic Shock Database Research Group. (2014).	Retrospective analysis, a multicenter, observational study IIIB	The study sought to determine how hospital mortality was influenced by combined use of these two treatments, and retrospectively analyzed data from 24 ICUs in three countries.	Potential bias due to its retrospective approach, and possibility of unreported cointerventions influenced results	Results showed that fluids and vasoactive agents had strong, interacting associations with mortality ($p <$ 0.0001). Mortality was lowest when vasoactive agents were begun 1–6 hours after onset, with more than 1 L of fluids in the initial hour after shock onset, more than 2.4 L from hours 1–6, and 1.6–3.5 L from 6 to 24 hours. The lowest mortality rates were associated with starting vasoactive agents 1–6 hours after onset	the focus during the first hour of resuscitation for septic shock should be aggressive fluid administration, only thereafter starting vasoactive agents, while continuing aggressive fluid administration

Zhang, D., Micek, S. T., & Kollef, M. H. (2015).	Single-center retrospective cohort study IIIB	From January 2008 to December 2012, the study was conducted to assess the timing of AAT, included 1058 subjects in 1200-bed academic hospital. Timing of appropriate antibiotic therapy was determined from blood culture collection time to the administration of the first dose of antibiotic therapy with documented in vitro susceptibility against the identified pathogen	Retrospective study which limits causal inference	The median time from blood culture collection to the administration of AAT was 6.7 hours The time AAT is an independent determinant of postinfection ICU LOS; ($p < 0.001$) and postinfection hospital LOS increased per hr of time to deliver AAT; ($p < 0.001$). Other indep. determinants increasing ICU hospital LOS were mechanical ventilation and leukocytosis	time to appropriate antibiotic therapy in patients with sepsis to be an independent determinant of postinfection ICU and hospital lengths of stay. Clinicians should implement local strategies aimed at timely delivery of appropriate antibiotic therapy to improve outcomes and reduce the length of stay.

Kumar, A., Roberts, D., Wood, K. E., Light, B., Parrillo, J. E., Sharma, S., ... & Gurka, D. (2006).	Retrospective cohort study IIIB	Review of medical records of 2,731 adult patients with septic shock in fourteen intensive care units (four medical, four surgical, six mixed medical/surgical) and ten hospitals (four academic, six community) in Canada and the United States. Study sought to determine the prevalence and impact on mortality of delays in initiation of effective AAT from initial onset of hypotension of septic shock	Possible confounding factors may have played a role in outcomes Potential bias due to its retrospective approach, and possibility of unreported co-interventions influenced results	Among 2,154 septic shock patients (78.9% total) who received effective antimicrobial therapy only after the onset of recurrent or persistent hypotension, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted	Effective antimicrobial administration within the the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock

Quality rating as per Evidence table and quality guide by The Johns Hopkins Hospital/The Johns Hopkins University (Dearrholt, 2012); (Table B.1.).

APPENDIX B: EVIDENCE LEVEL AND QUALITY GUIDE

Table B.1. *Evidence Level and Quality Guide*

Evidence Levels	**Quality Guides**
Level I Experimental study, randomized controlled trial (RCT) Systematic review of RCTs, with or without meta-analysis	**A High quality:** Consistent, generalizable results; sufficient sample size for the study design; adequate control; definitive conclusions; consistent recommendations based on comprehensive literature review that includes thorough reference to scientific evidence
Level II Quasi-experimental study. Systematic review of a combination of RCTs and quasi-experimental, or quasi-experimental studies only, with or without meta-analysis	**B Good quality:** Reasonably consistent results; sufficient sample size for the study design; some control, fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence
Level III Non-experimental study Systematic review of a combination of RCTs, quasi-experimental and non-experimental studies, or non-experimental studies only, with or without meta-analysis Qualitative study or systematic review with or without a meta-synthesis	**C Low quality or major flaws:** Little evidence with inconsistent results; insufficient sample size for the study design; conclusions cannot be drawn

Level IV Opinion of respected authorities and/or nationally recognized expert committees/consensus panels based on scientific evidence Includes: □ Clinical practice guidelines □ Consensus panels	**A High quality:** Material officially sponsored by a professional, public, private organization, or government agency; documentation of a systematic literature search strategy; consistent results with sufficient numbers of well-designed studies; criteria-based evaluation of overall scientific strength and quality of included studies and definitive conclusions; national expertise is clearly evident; developed or revised within the last 5 years **B Good quality:** Material officially sponsored by a professional, public, private organization, or government agency; reasonably thorough and appropriate systematic literature search strategy; reasonably consistent results, sufficient numbers of well-designed studies; evaluation of strengths and limitations of included studies with fairly definitive conclusions; national expertise is clearly evident; developed or revised within the last 5 years **C Low quality or major flaws:** Material not sponsored by an official organization or agency; undefined, poorly defined, or limited literature search strategy; no evaluation of strengths and limitations of included studies, insufficient evidence with inconsistent results, conclusions cannot be drawn; not revised within the last 5 years.
Level V Based on experiential and non-research evidence Includes: □ Literature reviews □ Quality improvement, program or financial evaluation □ Case reports □ Opinion of nationally recognized experts(s) based on experiential evidence	**Organizational Experience:** **A High quality:** Clear aims and objectives; consistent results across multiple settings; formal quality improvement, financial or program evaluation methods used; definitive conclusions; consistent recommendations with thorough reference to scientific evidence **B Good quality:** Clear aims and objectives; consistent results in a single setting; formal quality improvement or financial or program evaluation methods used; reasonably consistent recommendations with some reference to scientific evidence **C Low quality or major flaws:** Unclear or missing aims and objectives; inconsistent results; poorly defined quality improvement, financial or program evaluation methods; recommendations cannot be made **Literature Review, Expert Opinion, Case Report, Community Standard,** **Clinician Experience, Consumer Preference:** **A High quality:** Expertise is clearly evident; draws definitive conclusions; provides scientific rationale; thought leader(s) in the field **B Good quality:** Expertise appears to be credible; draws fairly definitive conclusions; provides logical argument for opinions **C Low quality or major flaws:** Expertise is not discernable or is dubious; conclusions cannot be drawn

© The Johns Hopkins Hospital/The Johns Hopkins University
(Dearrholt, 2012)

APPENDIX C: MICROORGANISMS ASSOCIATED WITH RISK OF MORTALITY

Table C.1. *Type of Organisms Associated with Risk of Mortality*

Organism	**Frequency (%)**	**OR (95% CI)**
Gram-positive	46.8	
Staphylococcus aureus	20.5	0.8 (0.6–1.1)
MRSA	10.2	1.3 (0.9–1.8)
Enterococcus	10.9	1.6 (1.1–2.3)
S. epidermidis	10.8	0.9 (0.7–1.1)
S. pneumonia	4.1	0.8 (0.5–1.4)
Other	6.4	0.9 (0.7–1.2)
Gram-negative	62.2	
Pseudomonas species	19.9	1.4 (1.2–1.6)
Escherichia coli	16.0	0.9 (0.7–1.1)
Klebsiella species	12.7	1.0 (0.8–1.2)
Acinetobacter species	8.8	1.5 (1.2–2.0)
Enterobacter	7.0	1.2 (0.9–1.6)
Other	17.0	0.9 (0.7–1.3)
Anaerobes	4.5	0.9 (0.7–1.3)
Other bacteria	1.5	1.1 (0.6–2.0)
Fungi		
Candida	17.0	1.1 (0.9–1.3)
Aspergillus	1.4	1.7 (1.0–3.1)
Other	1.0	1.9 (1.0–3.8)
Parasites	0.7	1.3 (0.5–3.3)
Other organisms	3.9	0.9 (0.6–1.3)

OR, odds ratio; CI, confidence interval; MRSA, methicillin-resistant *S. aureus* (Mayr, Yende, & Angus, 2014).

APPENDIX D: PDCA TEMPLATE AND PDSA WORKSHEET

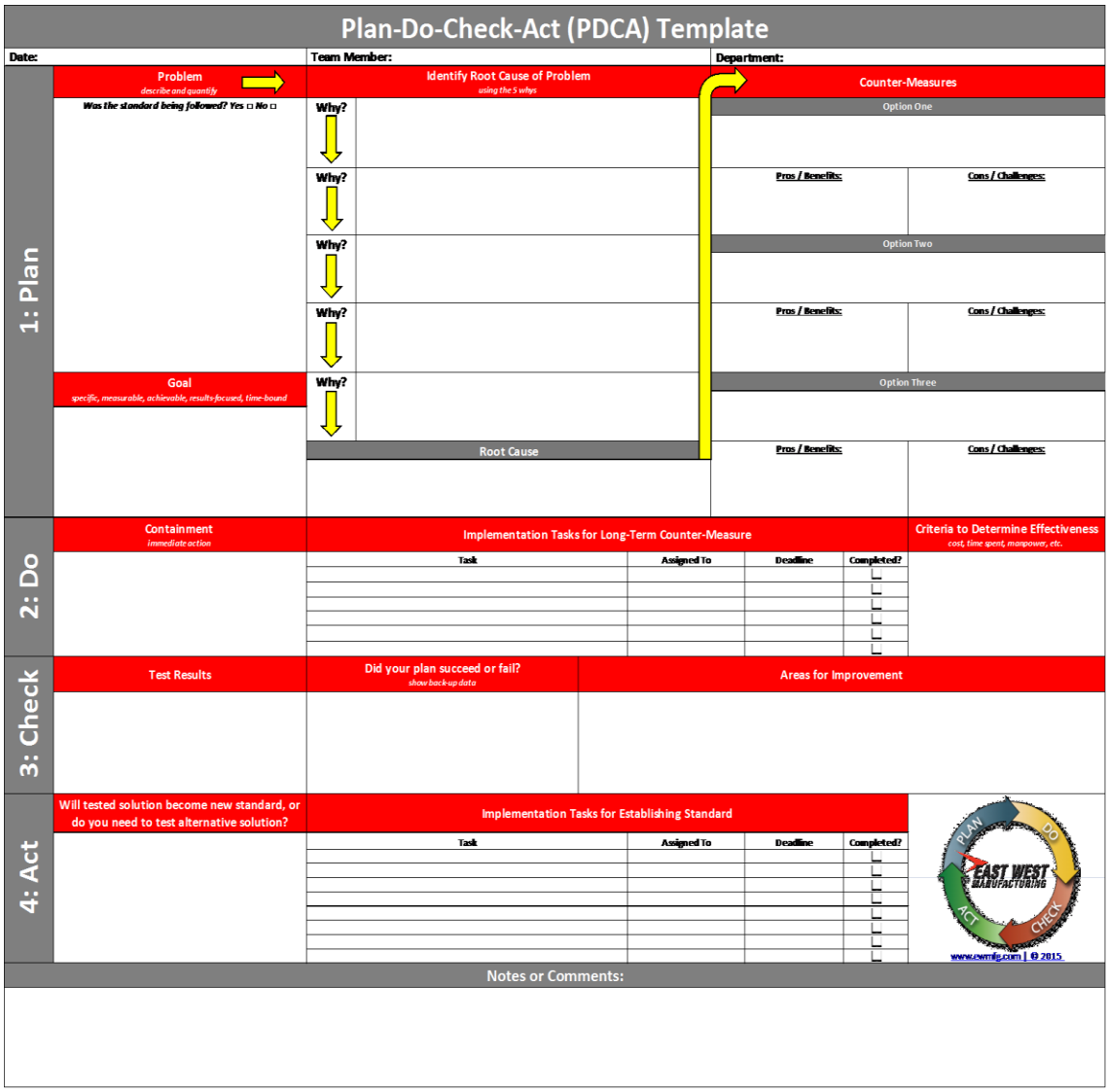
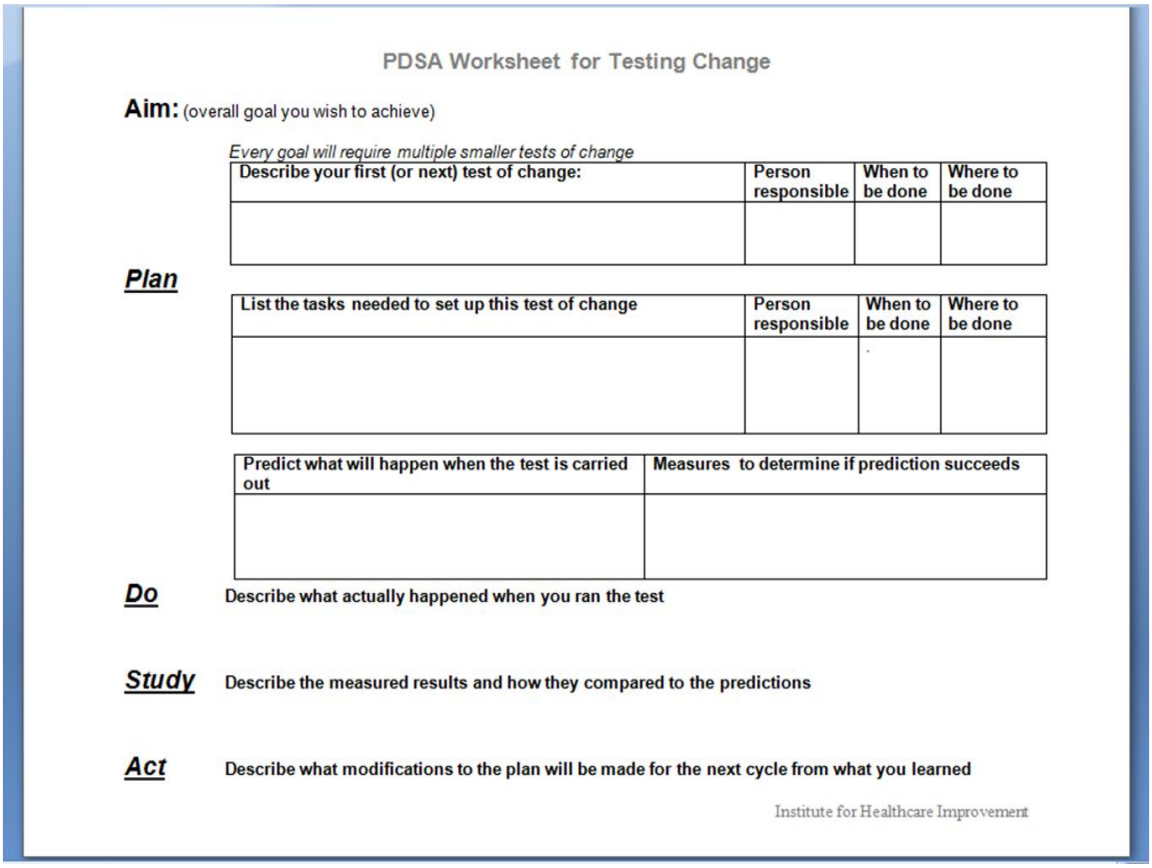


Figure D.1. PDCA Template
Source: Free resources, East West Manufacturing Company
http://www.ewmfg.com/resources



PDSA Worksheet for Testing Change

Aim: (overall goal you wish to achieve)

Every goal will require multiple smaller tests of change

Describe your first (or next) test of change:	Person responsible	When to be done	Where to be done

Plan

List the tasks needed to set up this test of change	Person responsible	When to be done	Where to be done

Predict what will happen when the test is carried out	Measures to determine if prediction succeeds

Do Describe what actually happened when you ran the test

Study Describe the measured results and how they compared to the predictions

Act Describe what modifications to the plan will be made for the next cycle from what you learned

Institute for Healthcare Improvement

Figure D.2. PDSA Worksheet
(Institute for Healthcare Improvement, 2014).

APPENDIX E: DATA COLLECTION ITEMS

Table E.1. *Data Collection Items*

<table>
<tr><td>Patient's unique # (PtID)
1,2,3,4,5,6,7,8,9…</td><td>Appropriate ABT for Dx (AbtAppr)
1 yes;
2 no</td></tr>
<tr><td>Age:
number of years</td><td>IVF (IVF1-3)
1 yes 30 ml/hr;
2: no;
3: contraindicated</td></tr>
<tr><td>Gender
1 male
2 female</td><td>Lactic Acid 1st drawn w/in 3 hrs (LA1_3h)
1-yes,
2 - no</td></tr>
<tr><td rowspan="2">Race (Race1-6)
1 Caucasian
2 African American
3 Asian
4 Hispanic
5 Native American;
6 Other</td><td>Lactic Acid sample #1 > 2 (LA1>2)
1 yes
2 no
0 not done</td></tr>
<tr><td>Repeat Lactic Acid 6 hrs (LA2_6h)
1 yes
2 no;
0 N/A, not indicated</td></tr>
<tr><td>LOS (Length of stay in # of days)
number of days spent in hospital</td><td rowspan="2">Blood Cultures (Cult<3h) (0-2)
1 yes <3h cultures drawn prior to administration of antibiotics
2 no >3h blood cultures drawn/ or not before antibiotics
0 -- Blood cultures were not done</td></tr>
<tr><td>Outcomes
Mortality (OutcMort)
1 yes - Alive
2 no - Deceased</td></tr>
<tr><td rowspan="2">Functional status at discharge (OutcFS 0-3)
0 same as pre-hospitalization
1 worse, lost independence, needs more help, declined
2 better than prior to hospitalization
3 Deceased</td><td>Cultures (Cult#hrID)
number of hr pathogen group described or identified in sample</td></tr>
<tr><td>Cultures (Cult#hrFIN)
number of hours final results of cultures known, including MIC</td></tr>
</table>

Discharge (D/C1-6) Discharge to: 1 Prior living situation/home, independent 2 Extended care facility/ SNF (new) 3 Deceased 4 Higher level of care (transfer to another hosp) 5 Home w/ Home Health/caregivers/more help 6 Discharged to Hospice	**Culture results: (CR0-5)** 0 negative cultures 1 positive cultures: bacteria 2 positive cultures: fungal 3 positive cultures: viral 4 positive cultures other 5 unknown
	C-diff 1 yes 2 no
Immune status impairing diagn (ImDx0-2) 0 – Immunocompetent (ImDx0) 1 – Immunocompromised with one Dx likely affecting immune status 2 – Immunocompromised with two or more Dx likely affecting immune status	**Site of positive cultures (P+1-9)** 1 blood 2 urine 3 wound 4 sputum 5 stool 6 CNS fluid 7 Pleural fluid 8 Peritoneal; 9 other
Dx: (ImmDx0-7) 0 None *(ImDx0)* 1 Ca, *(ImDx1)* 2 transplant/ spleenless *(ImDx2)* 3 COPD, *(ImDx3) etc*.. 4 DM 5 RA- on prednisone 6 Chemotherapy 7 other	**PATHOGEN:** **Gram negative pathogen (Gn1-12)** 1 E-coli 2 Klebsiella pneumoniae 3 Enterobacter 4 Acinetobacter 5 Pseudomonas aeruginosa 6 Proteus 7 Serratia 8 Morganella 9 Haemophilus influenzae 10 Campylobacter 11 Neisseria 12 other **Gram positive pathogen (G(+)1-13)** 1 Staph aureus MSSA 2 Staph aureus MRSA 3 Staph coagulase (-) epidermidis 4 Streptococcus pneumococcus 5 Strep viridians 6 Strep group A pyrogens 7 Corynebacterium 8 Enterococcus faecium 9 Enterococcus faecalis 10 Clostridum 11 Corynobacterium 12 Bacillus 13 other
Comorbidities (Cmb0-15) 0 None *(Cmb0)* 1 Ca *(Cmb1) etc*.. 2 COPD 3 DM 4 CAD 5 Malnutrition 6 ETOH chronic 7 Readmitted, recurrent infection 8 h/o sepsis 9 h/o MDR infection 10 Underlying dementia 11 ESRD on dialysis 12 Obesity 13 CHF 14 PVD 15 Other	

<table>
<tr>
<td>Initial presentation (IniPres1-3)
1 Sepsis
2 Severe Sepsis
3 Septic shock</td>
<td rowspan="2">Atypicals (Atyp1-3)
1 Mycoplasma
2 Chlamydia
3 Ricketts
Other
1 Viral (OthVir
2 Fungal (OthFung)</td>
</tr>
<tr>
<td>Acute mental status change (AMS)
1 yes
2 no</td>
</tr>
<tr>
<td>Sepsis cause (SCs1-13)
1 Pneumonia (SCs1)
2 UTI (SCs2) etc
3 Pyelonephritis
4 GI/intraabdominal
5 Skin (Cellulitis)
6 Post- Surgery complications
7 Wound infection
8 Meningitis
9 other
10 Neutropenic Fever
11FUO
12 Bacteremia
13 Osteomyelitis</td>
<td>MDR Organisms (MDR1-6)
1 MRSA
2 VRE
3 CRE
4 C-diff
5 ESBL
6 Other</td>
</tr>
<tr>
<td>Hospital course (Hcr1-3)
1 ICU w/ pressors and mechanical ventilation
2 ICU w/o mechanical ventilation
3 no pressors, no vent, PCU/other

Progression of Sepsis
1 yes - worse: severe sepsis progressed to septic shock despite tx (or death)
2 no – better, status did not deteriorate during hospitalization

Treatment w/ initial Antibiotics (Abt<3h)
1 Yes: <3h from time 0 first antibiotic administered* (not ordered)
2 No: >3h from time 0 first abt administered*

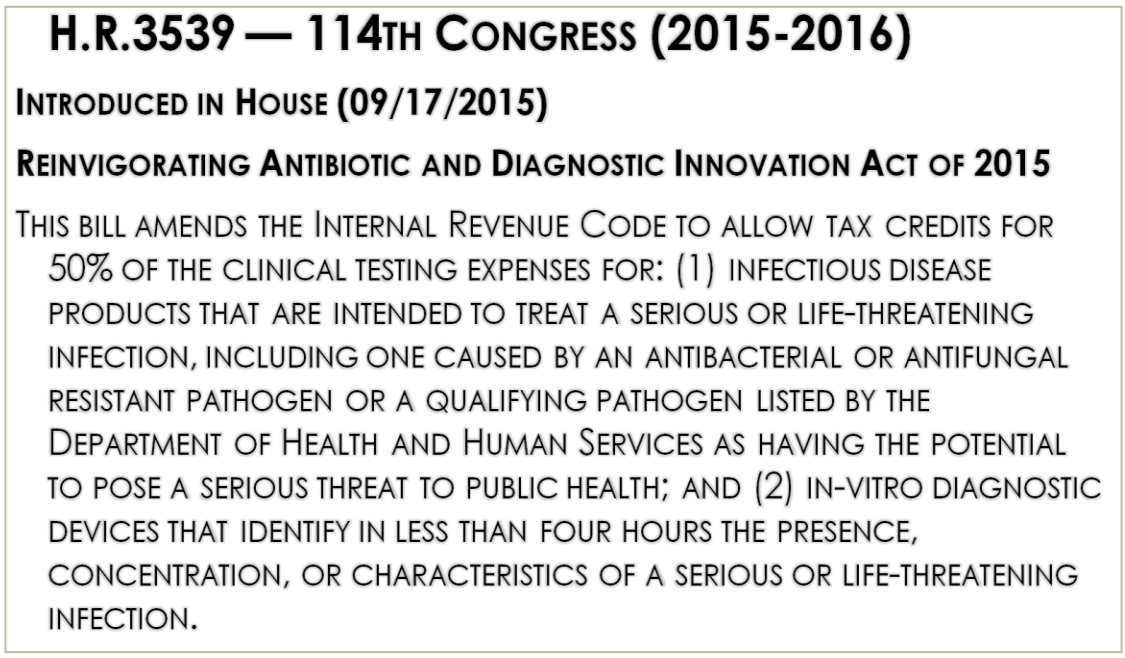
Days on Abt (AbtEmp#D)
number of days on empiric antibiotics

Number of empiric antibiotics (AbtEmp#)
#number of prescribed antibiotic

ABT Deescalated: (AbtDesc)
1 - yes
2- no</td>
<td>Antimicrobial class (Ab1-21)
1 – PCN (Ab1)
2 – Extended PCN (Zosyn) (Ab2)
3 – B-lactamase inh PCN (Unasyn) (Ab3)etc..
4 – Cephalosporin 1st
5 – Cephalosporin 2nd
6 – Cephalosporin 3rd
7 – Cephalosporin 4th
8 – Cephalosporin 5th (Ceftaroline)
9 – Fluoroquinolone 2nd (Cipro)
10 – Quinolone 3rd (Lavo/Moxi)
11 – Macrolides
12 – Tetracycline
13 – Sulfonamides
14 – Carbapenems
15 – Monobactam (Aztreonam)
16 – Glycopeptide (Vanc)
17 – Liptopeptide (Cubicin/Dapto)
18 – Oxazolidinone (Zyvox/linezolid)
19 – Lincosamide (Clindamycin)
20 – Other antibiotics (Tigecycline)
21 – Nitroimidazole (Flagyl)</td>
</tr>
<tr>
<td>Complications (cmp1-11)
1 C-diff
2 MDR organism
3 Surgery
4 Neutropenia
5 Coagulopathy</td>
<td>Other Treatment (OthTx 1-3)
1 – Antifungal (fluconazole)
2 – Antiviral
3 – Other atypical</td>
</tr>
</table>

6 Abscess 7 Renal failure 8 Respiratory failure 9 Multisystem failure 10 Cardiac complications 11 Other	
Potential costs savings On LOS **(Sav$LOS)** 1 yes; 2 no On ABT de-escalation **(Sav$Abt)** 1 yes; 2 no	**Appropriate antibiotic for culture results (AbtAppr)** 1 Yes; 2 No
Readmitted w/in 30 days (Readm30) 1 yes; 2 no	**Healthcare Acquired infection (HCaq)** 1 yes; 2 No

APPENDIX F: CONGRESSIONAL BILL



H.R.3539 — 114TH CONGRESS (2015-2016)

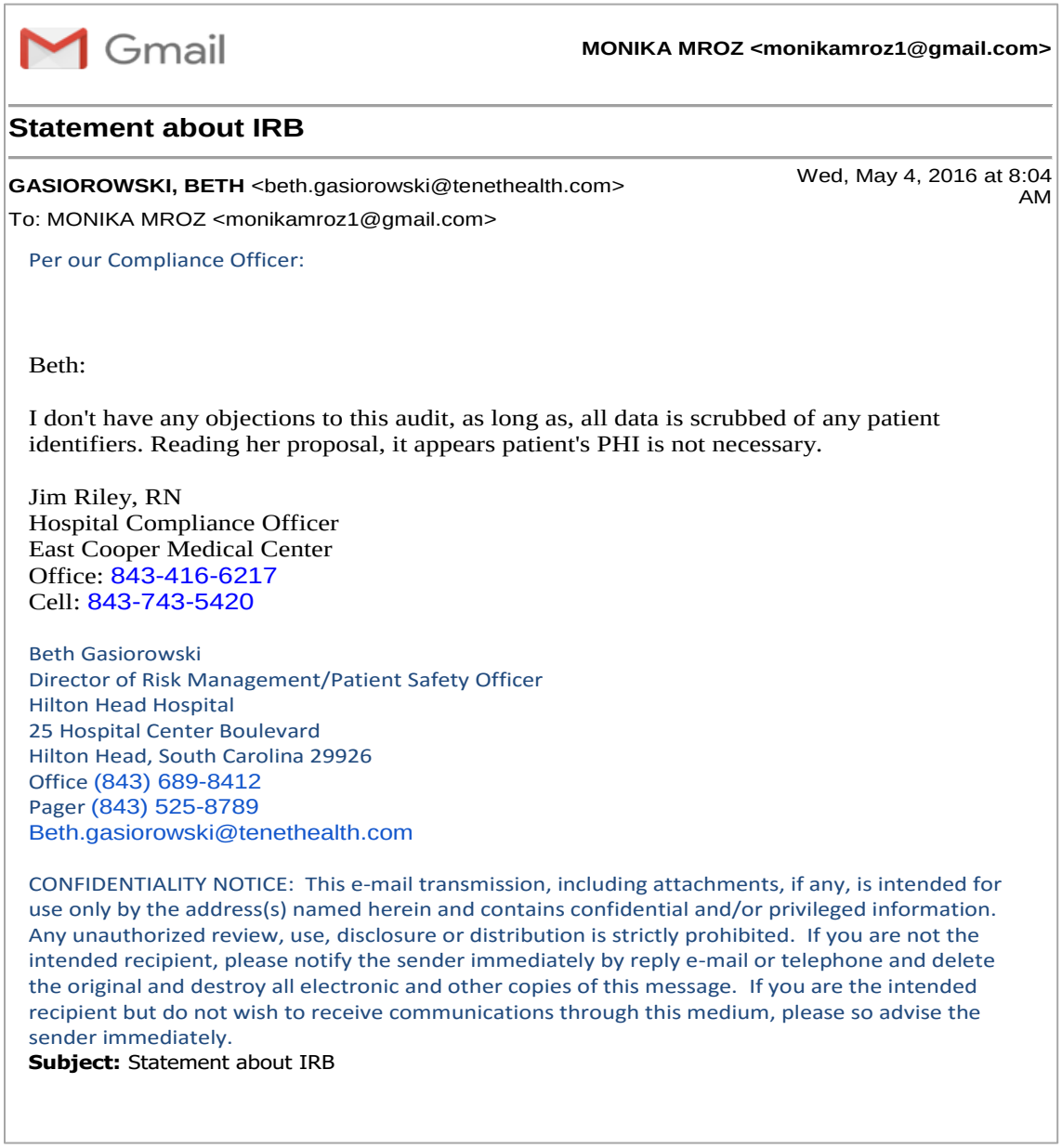
INTRODUCED IN HOUSE (09/17/2015)

REINVIGORATING ANTIBIOTIC AND DIAGNOSTIC INNOVATION ACT OF 2015

THIS BILL AMENDS THE INTERNAL REVENUE CODE TO ALLOW TAX CREDITS FOR 50% OF THE CLINICAL TESTING EXPENSES FOR: (1) INFECTIOUS DISEASE PRODUCTS THAT ARE INTENDED TO TREAT A SERIOUS OR LIFE-THREATENING INFECTION, INCLUDING ONE CAUSED BY AN ANTIBACTERIAL OR ANTIFUNGAL RESISTANT PATHOGEN OR A QUALIFYING PATHOGEN LISTED BY THE DEPARTMENT OF HEALTH AND HUMAN SERVICES AS HAVING THE POTENTIAL TO POSE A SERIOUS THREAT TO PUBLIC HEALTH; AND (2) IN-VITRO DIAGNOSTIC DEVICES THAT IDENTIFY IN LESS THAN FOUR HOURS THE PRESENCE, CONCENTRATION, OR CHARACTERISTICS OF A SERIOUS OR LIFE-THREATENING INFECTION.

Figure F.1. Bill H.R.3539 - 114th Congress (2015-1016)

APPENDIX G: IRB STATEMENT



Gmail MONIKA MROZ <monikamroz1@gmail.com>

Statement about IRB

GASIORowski, BETH <beth.gasiorowski@tenethealth.com> Wed, May 4, 2016 at 8:04 AM

To: MONIKA MROZ <monikamroz1@gmail.com>

Per our Compliance Officer:

Beth:

I don't have any objections to this audit, as long as, all data is scrubbed of any patient identifiers. Reading her proposal, it appears patient's PHI is not necessary.

Jim Riley, RN
Hospital Compliance Officer
East Cooper Medical Center
Office: 843-416-6217
Cell: 843-743-5420

Beth Gasiorowski
Director of Risk Management/Patient Safety Officer
Hilton Head Hospital
25 Hospital Center Boulevard
Hilton Head, South Carolina 29926
Office (843) 689-8412
Pager (843) 525-8789
Beth.gasiorowski@tenethealth.com

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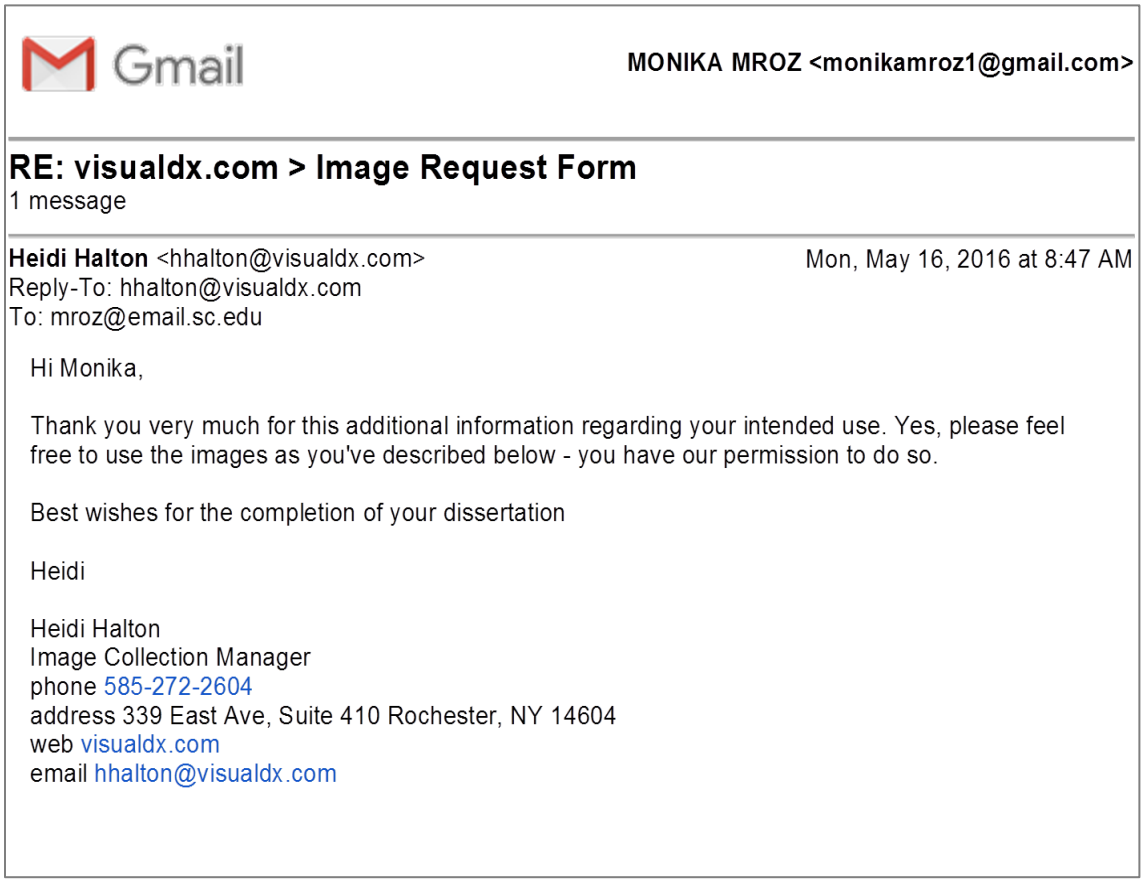
Subject: Statement about IRB

Figure G.1. IRB Statement
A screenshot of the email received from the Safety Officer /Director of Risk Management as per the Compliance officer.

APPENDIX H: PERMISSION TO USE IMAGES



Gmail MONIKA MROZ <monikamroz1@gmail.com>

RE: visualdx.com > Image Request Form
1 message

Heidi Halton <hhalton@visualdx.com> Mon, May 16, 2016 at 8:47 AM
Reply-To: hhalton@visualdx.com
To: mroz@email.sc.edu

Hi Monika,

Thank you very much for this additional information regarding your intended use. Yes, please feel free to use the images as you've described below - you have our permission to do so.

Best wishes for the completion of your dissertation

Heidi

Heidi Halton
Image Collection Manager
phone 585-272-2604
address 339 East Ave, Suite 410 Rochester, NY 14604
web visualdx.com
email hhalton@visualdx.com

Figure H.1. Permission to use images
A screenshot of the email received from the manager of Image Collection at VisualDx.com

APPENDIX I: ICD-10-CM DIAGNOSIS CODES

Diagnosis codes included in reports:

- Other sepsis A41
- postprocedural sepsis (T81.4)
- sepsis following immunization (T88.0)
- sepsis following infusion, transfusion or therapeutic injection (T80.2-)
- sepsis (due to) (in) actinomycotic (A42.7)
- sepsis (due to) (in) anthrax (A22.7)
- sepsis (due to) (in) candidal (B37.7)
- sepsis (due to) (in) Erysipelothrix (A26.7)
- sepsis (due to) (in) extraintestinal yersiniosis (A28.2)
- sepsis (due to) (in) gonococcal (A54.86)
- sepsis (due to) (in) herpesviral (B00.7)
- sepsis (due to) (in) listerial (A32.7)
- sepsis (due to) (in) melioidosis (A24.1)
- sepsis (due to) (in) meningococcal (A39.2-A39.4)
- sepsis (due to) (in) plague (A20.7)
- sepsis (due to) (in) tularemia (A21.7)
- toxic shock syndrome (A48.3)

Additional codes included:

- A41 Other sepsis
- A41.0 Sepsis due to Staphylococcus aureus
- A41.01 Sepsis due to Methicillin susceptible Staphylococcus aureus
- A41.02 Sepsis due to Methicillin-resistant Staphylococcus aureus
- A41.1 Sepsis due to other specified staphylococcus
- A41.2 Sepsis due to unspecified staphylococcus
- A41.3 Sepsis due to Hemophilus influenzae
- A41.4 Sepsis due to anaerobes
- A41.5 Sepsis due to other Gram-negative organisms
- A41.50 Gram-negative sepsis, unspecified
- A41.51 Sepsis due to Escherichia coli [E. coli]
- A41.52 Sepsis due to Pseudomonas
- A41.53 Sepsis due to Serratia
- A41.59 Other Gram-negative sepsis
- A41.8 Other specified sepsis
- A41.81 Sepsis due to Enterococcus
- A41.89 Other specified sepsis
- A41.9 Sepsis, unspecified organism
- sepsis NOS (A41.9)
- streptococcal sepsis (A40.-)

Diagnosis codes excluded from reports:

- sepsis during labor (O75.3)
- sepsis following abortion, ectopic or molar pregnancy (O03-O07, O08.0)
- bacteremia NOS (R78.81)
- neonatal (P36.-)
- puerperal sepsis (O85)

Source: ICD10Data.com

(2016 ICD-10-CM Diagnosis Codes A41.* : Other sepsis A41)

APPENDIX J: EXAMPLES OF DATA COLLECTION WORKSHEETS SET

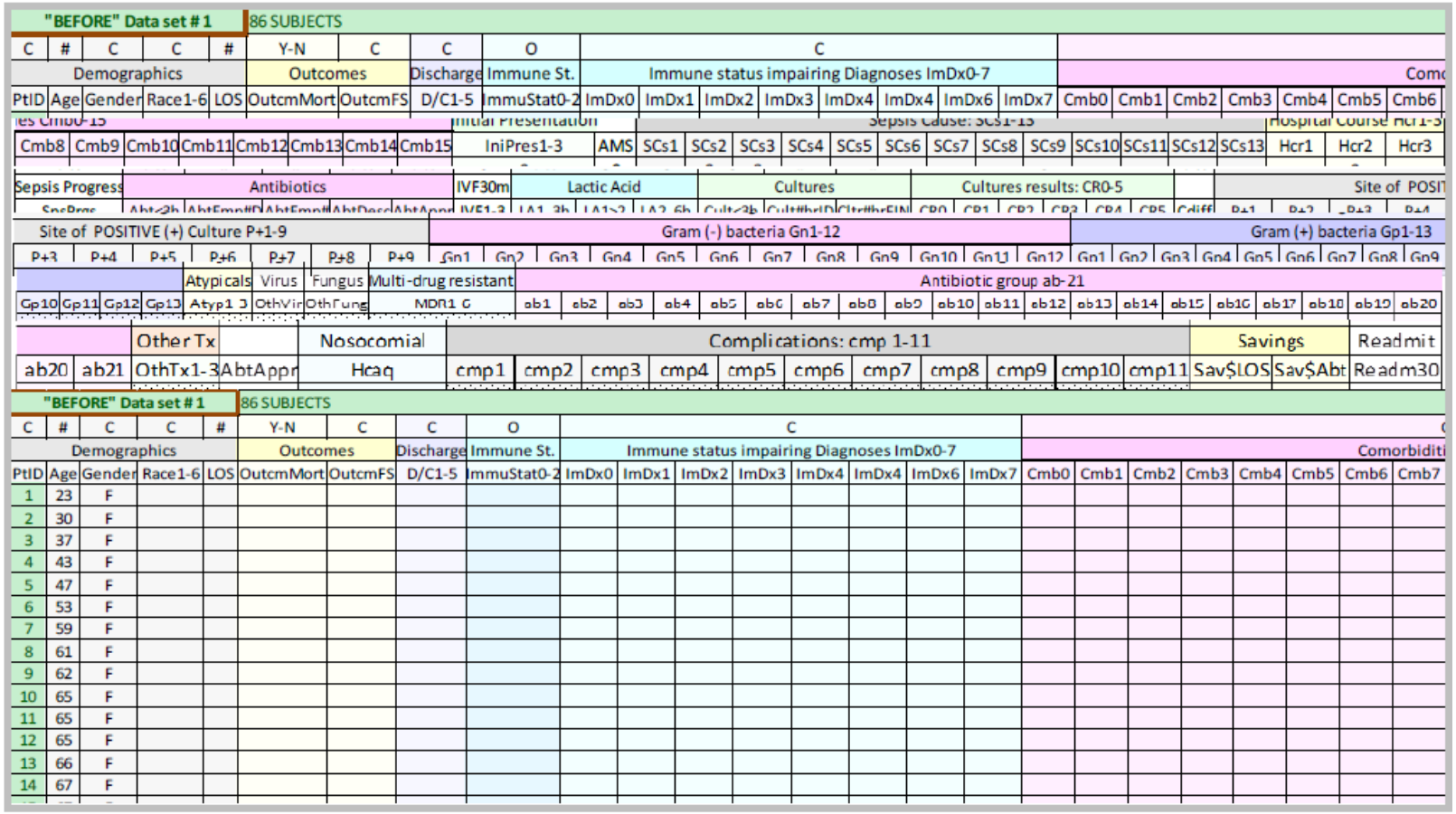


Figure J.1. Data collection worksheets
Worksheet column headings shown, coded variables for raw data, created using Excel®.

Legend:

Patient's unique # (PtID) --CATEGORICAL
1,2,3,4,5,6,7,8,9…
Age: --NUMERIC
number of years
Gender --CATEGORICAL
1 male 2 female
Race (Race1-6) --CATEGORICAL
1 Caucasian
2 African American
3 Asian
4 Hispanic
5 Native America; or: 6 Other
LOS (Length of stay in # of days) --NUMERIC
number of days spent in hospital
Outcomes
Mortality **(OutcMort) YES-NO Yes=1 No=2**
1 yes – Alive 2 no - Deceased
Functional status at discharge (OutcFS 0-3) --CATEGORICAL
0 same as pre-hospitalization
1 worse, lost independence, needs more help, declined
2 better then prior to hospitalization
3 Deceased
Discharge (D/C1-6) --CATEGORICAL
Discharge to:
1 Prior living situation/home, independent
2 Extended care facility/ SNF (new)
3 Deceased
4 Higher level of care (transfer to another hospital)
5 Home w/ Home Health/caregivers/more help
6 Discharged to Hospice
Immune status impairing diagnoses (ImDx0-2) --ORDINAL
0 – Immunocompetent (ImDx0)
1 – Immunocompromised with one Dx likely affecting immune status
2 – Immunocompromised with two or more Dx affecting status
Dx: (ImmDx0-7) --CATEGORICAL
0 None *(ImDx0)*
1 Ca, *(ImDx1)*
2 transplant/ spleenless *(ImDx2)*
3 COPD, *(ImDx3) etc.*.
4 DM
5 RA- on prednisone
6 Chemotherapy; or: 7 other
Comorbidities (Cmb0-15) --CATEGORICAL
0 None *(Cmb0)*
1 Ca *(Cmb1) etc.*.
2 COPD
3 DM
4 CAD
5 Malnutrition
6 ETOH chronic
7 Readmitted, recurrent infection
8 h/o sepsis
9 h/o MDR infection
10 Underlying dementia
11 ESRD on dialysis
12 Obesity
13 CHF
14 PVD; or: 15 Other
Initial presentation (IniPres1-3) --ORDINAL
1 Sepsis
2 Severe Sepsis
3 Septic shock
Acute mental status change (AMS) --YES-NO Yes=1 No=2
1 yes 2 no
Sepsis cause (SCs1-13) --CATEGORICAL
1 Pneumonia *(SCs1)*
2 UTI *(SCs2) etc*
3 Pyelonephritis
4 GI/intraabdominal
5 Skin (Cellulitis)

6 Post- Surgery complications
7 Wound infection
8 Meningitis;
10 Neutropenic Fever
11FUO
12 Bacteremia
13 Osteomyelitis; or: 9 other

Hospital course (Hcr1-3) --CATEGORICAL
1 ICU w/ pressors and mechanical ventilation
2 ICU w/o mechanical ventilation
3 no pressors, no vent, PCU/other

Progression of Sepsis -- YES-NO Yes=1 No=2
1 yes - worse: severe sepsis progressed to septic shock or death
2 no – better, status did not deteriorate during hospitalization

Treatment w/ initial Antibiotics (Abt<3h) Yes=1 No=2
1 Yes: <3h from time 0 first antibiotic administered* (not ordered)
2 No: >3h from time 0 first antibiotic administered*

Days on Abt --NUMERIC
number of days on empiric antibiotics **(AbtEmp#D)**

Number of empiric antibiotics (AbtEmp#) --NUMERIC
#number of prescribed antibiotic

ABT Deescalated: (AbtDesc) Yes=1 No=2
1 – yes 2- no

Appropriate ABT for Dx (AbtAppr) Yes=1 No=2
1 – yes 2 no

IVF (IVF1-3) --CATEGORICAL
1 yes 30 ml/hr 2 no 3 contraindicated

Lactic Acid 1st drawn w/in 3 hrs **(LA1_3h) Yes=1 No=2**
1-yes, 2 - no

Lactic Acid sample #1 > 2 (LA1>2) --CATEGORICAL
1 yes 2 no 0 not done

Repeat Lactic Acid 6 hrs (LA2_6h) --CATEGORICAL
1 yes 2 no 0 N/A, not indicated

Cultures (Cult<3h) --CATEGORICAL
1 yes <3h &BLOOD cultures drawn prior to admof antibiotic
2 no >3h &BLOOD cultures drawn/ or not before administration of antibiotic
0 -- Blood cultures were not done

Cultures (Cult#hrID) --NUMERIC
number of hr pathogen group described or identified in sample **NUMERIC**

Cultures (Cult#hrFIN) --NUMERIC
number of hours final results of cultures known, including MIC

Culture results: (CR0-5) --CATEGORICAL
0 negative cultures
1 positive cultures: bacteria
2 positive cultures: fungal
3 positive cultures: viral
4 positive cultures other; or:5 unknown

C-diff --YES-NO Yes=1 No=2
1 yes 2 no

Site of positive cultures (P+1-9) --CATEGORICAL
1 blood
2 urine
3 wound
4 sputum
5 stool
6 CNS fluid
7 Pleural fluid
8 Peritoneal; or: 9 other

PATHOGEN:

Gram negative pathogen (Gn1-12) --CATEGORICAL
1 E-coli
2 Klebsiella pneumoniae
3 Enterobacter
4 Acinetobacter
5 Pseudomonas aeruginosa
6 Proteus
7 Serratia
8 Morganella
9 Haemophilus influenzae
10 Campylobacter
11 Neisseria; or: 12 other

Gram positive pathogen (G(+)1-13) --CATEGORICAL

1 Staph aureus MSSA
2 Staph aureus MRSA
3 Staph coagulase (-) epidermidis
4 Streptococcus pneumococcus
5 Strep viridians
6 Strep group A pyrogens
7 Corynebacterium
8 Enterococcus faecium
9 Enterococcus faecalis
10 Clostridum
11 Corynobacterium
12 Bacillus; or: 13 other

Atypicals (Atyp1-3) --CATEGORICAL
1 Mycoplasma
2 Chlamydia
3 Ricketts

Other --CATEGORICAL
1 Viral (OthVir
2 Fungal (OthFung)

MDR Organisms (MDR1-6) --CATEGORICAL
1 MRSA
2 VRE
3 CRE
4 C-diff
5 ESBL; or: 6 Other

Antimicrobial class (Ab1-21) --CATEGORICAL
1 – PCN *(Ab1)*
2 – Extended PCN (Zosyn) *(Ab2)*
3 – B-lactamase inh PCN (Unasyn) *(Ab3)etc.*.
4 – Cephalosporin 1st
5 – Cephalosporin 2nd
6 – Cephalosporin 3rd
7 – Cephalosporin 4th
8 – Cephalosporin 5th (Ceftaroline)
9 – Fluoroquinolone 2nd (Cipro)
10 – Quinolone 3rd (Lavo/Moxi)
11 – Macrolides
12 – Tetracycline
13 – Sulfonamides
14 – Carbapenems
15 – Monobactam (Aztreonam)
16 – Glycopeptide (Vanc)
17 – Liptopeptide (Cubicin/Dapto)
18 – Oxazolidinone (Zyvox/linezolid)
19 – Lincosamide (Clindamycin)
20 – Other antibiotics (Tigecycline)
21 – Nitroimidazole (Flagyl)

Other Treatment (OthTx 1-3)
1 – Antifungal (fluconazole)
2 – Antiviral; 3 Other atypical

Appropriate antibiotic for culture results (AbtAppr)Yes=1 No=2
1 Yes; 2 No

Healthcare Acquired infection (HCaq) Yes=1 No=2
1 yes; 2 No

Complications (cmp1-11) --CATEGORICAL
1 C-diff
2 MDR organism
3 Surgery
4 Neutropenia
5 Coagulopathy
6 Abscess
7 Renal failure
8 Respiratory failure
9 Multisystem failure
10 Cardiac complications 11 Other

Potential costs savings On LOS **(Sav$LOS) Yes=1 No=2**
1 yes; 2 no
On ABT de-escalation **(Sav$Abt) Yes=1 No=2**
1 yes; 2 no

Readmitted w/in 30 days (Readm30) Yes=1 No=2
1 yes; 2 no

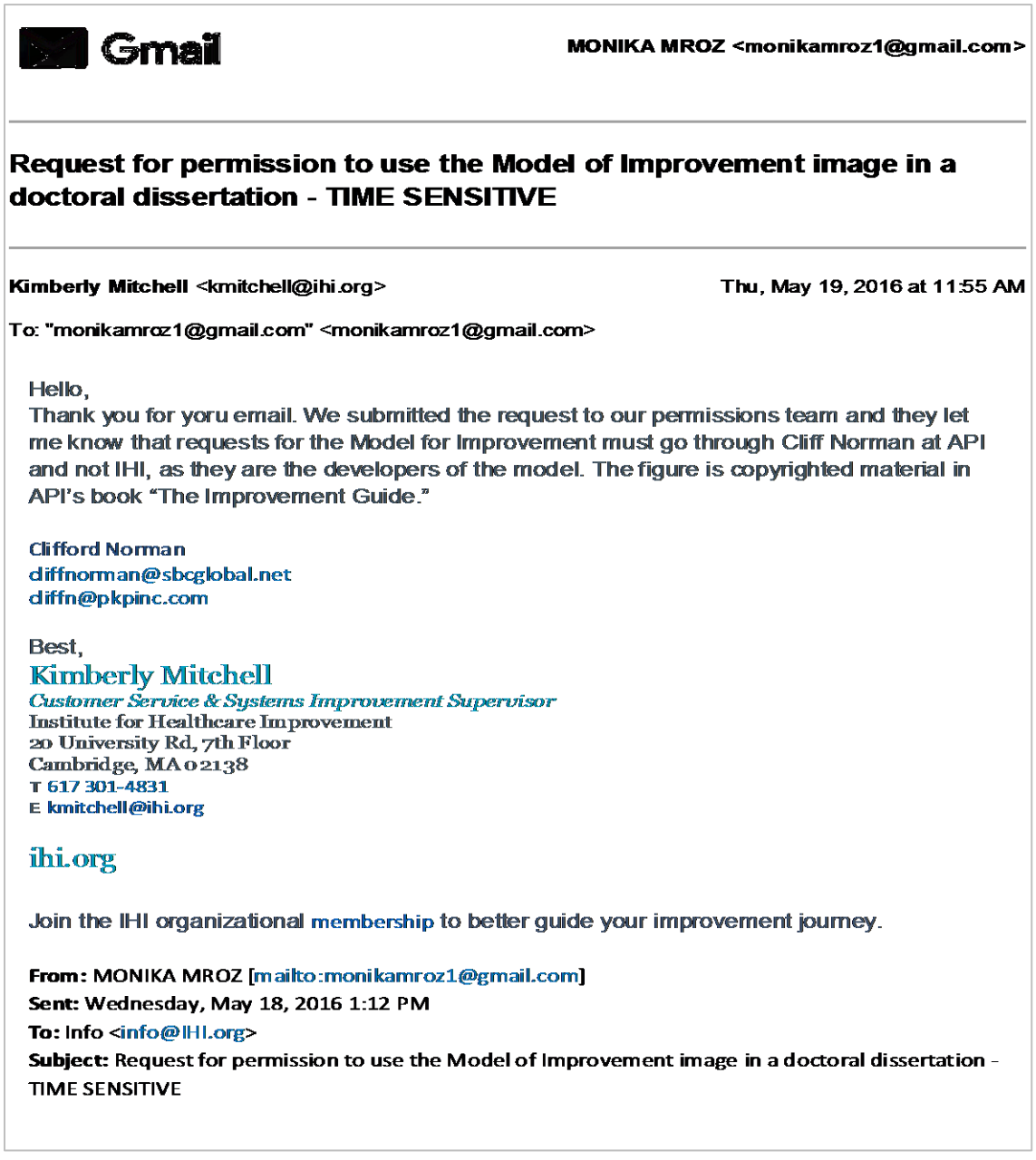
APPENDIX K: EXAMPLES OF VARIABLE CODING SYSTEM

Table K.1. *Variable Coding System*

Variable/category	**Code**	**Subcategory codes**
Patient's #	(PtID)	(#1, 2, 3, 4, 5…n)
Race	(Race1-6)	1=Caucasian: *Race1*; 2=African American: *Race2*; 3=Asian: *Race 3*; … *Race6*
Functional status at discharge	(OutcFS 0-3)	0=No change from pre-hospitalization: *OutcFS1*; 1=Worse, lost independence, declined: *OutcFS1*; 2=Better then prior to hospitalization: *OutcFS2*; 3=Deceased: *OutcFS3*
Discharge destination	(D/C1-6)	1=Prior living situation or home, independent: *D/C1*; 2=Extended care facility/ SNF (new): *D/C2*; 3=Deceased: *D/C3*; 4=Higher level of care, transfer to another hospital: *D/C4*; 5=Home with Home Health, requires more help: *D/C5*; 6=Discharged to Hospice: *D/C6*
Comorbidities	(Cmb0-15)	0=None: *Comb0*; 1=Cancer *Comb1*; 2=Chronic Obstructive Lung Disease *Comb2*; 3=Diabetes *Comb3; …Comb15*
Complications	(cmp1-11)	1=C-diff*: comp1*; 2=MDR organism*: comp2*; 3=Surgery*: comp3*; 4=Neutropenia*: comp4*; *…: comp11*)
Site of positive cultures	(P+1-9)	1=Blood*: P+1*; 2=Urine*: P+2*; 3=Wound*: P+3*; 4=Sputum*: P+4* l … *: P+9*
Gram negative pathogen	(Gn1-12)	1=E-coli: *Gn1*; 2=Klebsiella pneumonia: *Gn2*; 3=Enterobacter: *Gn2*; 4=Acinetobacter: *Gn4*; … : *Gn12*)
Gram positive pathogen	G(+)1-13)	1=Staph aureus MSSA: *G(+)1*; 2=Staph aureus MRSA: *G(+)2*; 3=Staph coagulase (-) epidermidis: *G(+)3* ; 4=Streptococcus pneumococcus: *G(+)4* ; … : *G(+)13*
Antimicrobial class	(Ab1-21)	1= PCN: *(Ab1)*; 2=Extended PCN: *Ab2*; 3=B-lactamase inh PCN: *Ab3; …Ab21*

APPENDIX L: PERMISSION TO REPRINT

Permission to reprint the PDSA Model for improvement



Gmail MONIKA MROZ <monikamroz1@gmail.com>

Request for permission to use the Model of Improvement image in a doctoral dissertation - TIME SENSITIVE

Kimberly Mitchell <kmitchell@ihi.org> Thu, May 19, 2016 at 11:55 AM

To: "monikamroz1@gmail.com" <monikamroz1@gmail.com>

Hello,
Thank you for yoru email. We submitted the request to our permissions team and they let me know that requests for the Model for Improvement must go through Cliff Norman at API and not IHI, as they are the developers of the model. The figure is copyrighted material in API's book "The Improvement Guide."

Clifford Norman
diffnorman@sbcglobal.net
diffn@pkpinc.com

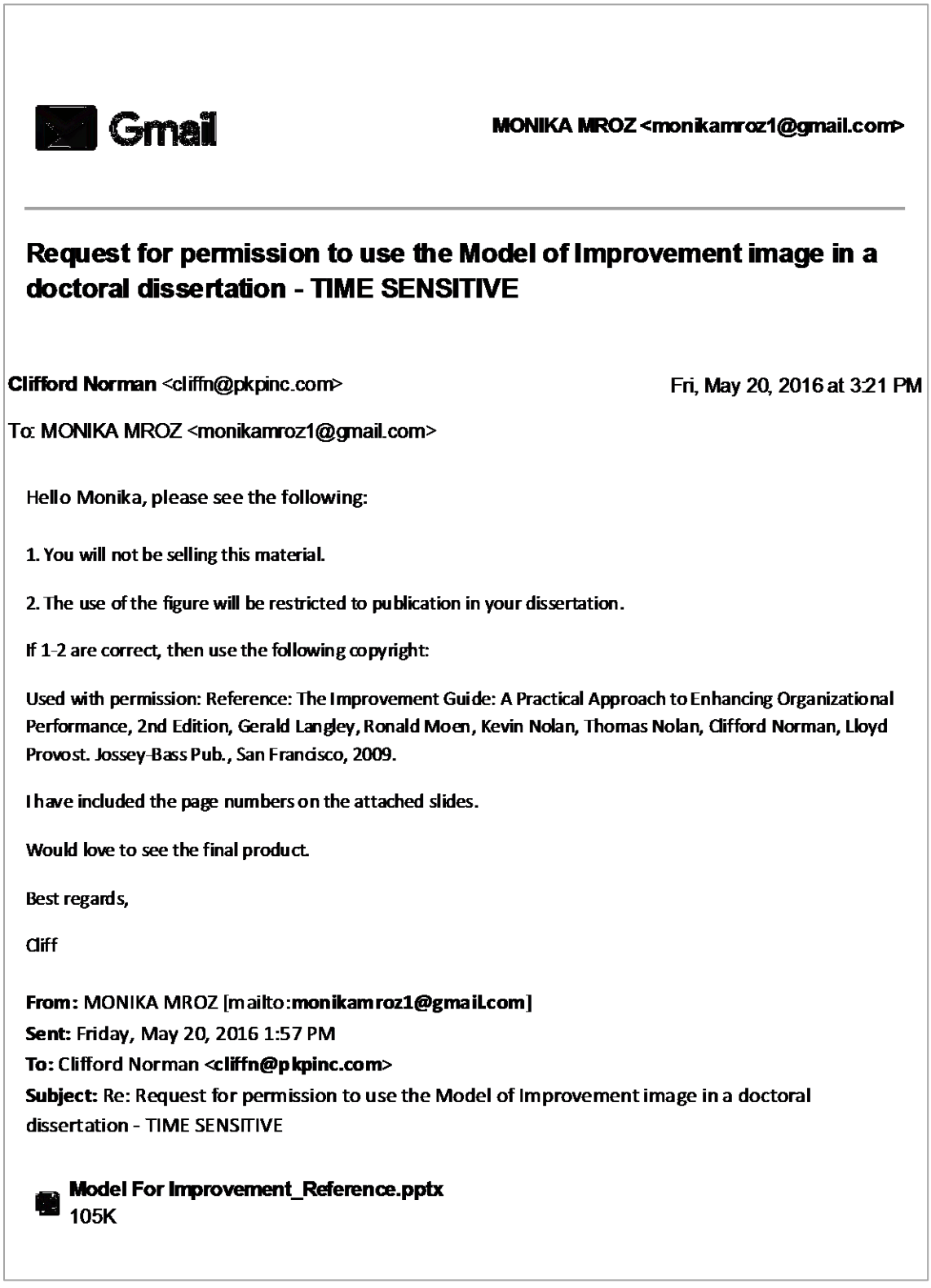
Best,
Kimberly Mitchell
Customer Service & Systems Improvement Supervisor
Institute for Healthcare Improvement
20 University Rd, 7th Floor
Cambridge, MA 02138
T 617 301-4831
E kmitchell@ihi.org

ihi.org

Join the IHI organizational membership to better guide your improvement journey.

From: MONIKA MROZ [mailto:monikamroz1@gmail.com]
Sent: Wednesday, May 18, 2016 1:12 PM
To: Info <info@IHI.org>
Subject: Request for permission to use the Model of Improvement image in a doctoral dissertation - TIME SENSITIVE

Figure L.1. Permission to reprint PDSA Model for improvement request



Gmail MONIKA MROZ <monikamroz1@gmail.com>

Request for permission to use the Model of Improvement image in a doctoral dissertation - TIME SENSITIVE

Clifford Norman <cliffn@pkpinc.com> Fri, May 20, 2016 at 3:21 PM

To: MONIKA MROZ <monikamroz1@gmail.com>

Hello Monika, please see the following:

1. You will not be selling this material.

2. The use of the figure will be restricted to publication in your dissertation.

If 1-2 are correct, then use the following copyright:

Used with permission: Reference: The Improvement Guide: A Practical Approach to Enhancing Organizational Performance, 2nd Edition, Gerald Langley, Ronald Moen, Kevin Nolan, Thomas Nolan, Clifford Norman, Lloyd Provost. Jossey-Bass Pub., San Francisco, 2009.

I have included the page numbers on the attached slides.

Would love to see the final product.

Best regards,

Cliff

From: MONIKA MROZ [mailto:**monikamroz1@gmail.com**]
Sent: Friday, May 20, 2016 1:57 PM
To: Clifford Norman <**cliffn@pkpinc.com**>
Subject: Re: Request for permission to use the Model of Improvement image in a doctoral dissertation - TIME SENSITIVE

Model For Improvement_Reference.pptx
105K

Figure L.2. Permission to reprint PDSA Model for improvement

APPENDIX M: DESCRIPTIVE STATISTICAL DATA

Mortality and Length of Stay Data

Table M.1. *Mortality by Age.*

OutcmMort	N	Mean	Std Dev	Std Err	Minimum	Maximum
Alive	108	72.3981	14.8103	1.4251	23.0000	97.0000
Deceased	50	78.1600	13.2532	1.8743	43.0000	97.0000
Diff (1-2)		-5.7619	14.3394	2.4528		

OutcMort	Method	Mean	95% CL Mean		Std Dev	95% CL Std Dev	
Alive		72.3981	69.5730	75.2233	14.8103	13.0640	17.0997
Deceased		78.1600	74.3935	81.9265	13.2532	11.0708	16.5153
Diff (1-2)	Pooled	-5.7619	-10.6069	-0.9169	14.3394	12.9095	16.1284
Diff (1-2)	Satterthwaite	-5.7619	-10.4301	-1.0936			

p<0.05. * T-Test Variable: OutcmMort: Mortality

Table M.2. *Mortality by LOS*

OutcmMort	N	Mean	Std Dev	Std Err	Minimum	Maximum
Alive	108	7.0556	4.8872	0.4703	1.0000	26.0000
Deceased	50	7.0800	5.8269	0.8240	1.0000	27.0000
Diff (1-2)		-0.0244	5.2007	0.8896		

OutcmMort	Method	Mean	95% CL Mean		Std Dev	95% CL Std Dev	
Alive		7.0556	6.1233	7.9878	4.8872	4.3110	5.6427
Deceased		7.0800	5.4240	8.7360	5.8269	4.8674	7.2611
Diff (1-2)	Pooled	-0.0244	-1.7816	1.7328	5.2007	4.6821	5.8495
Diff (1-2)	Satterthwaite	-0.0244	-1.9119	1.8630			

p=0.9. * T-Test: Variable: OutcmMort: Mortality; LOS: length of hospital stay.

Age in Relation To LOS and Mortality Between Groups

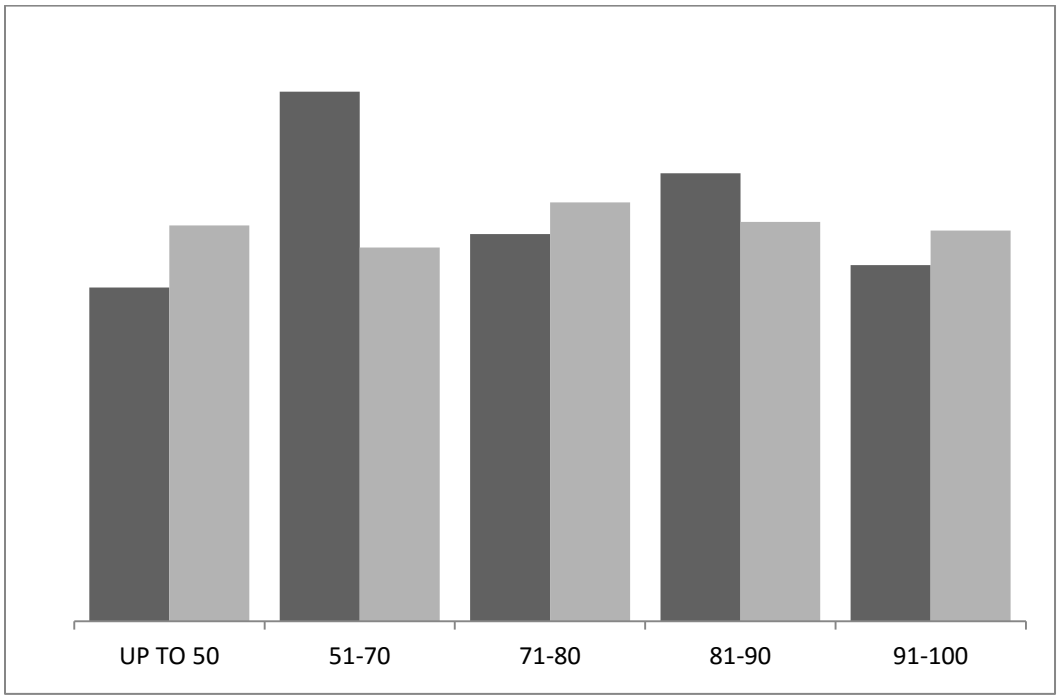


Figure M.1. Mortality by Age and Group.
*By age and groups: dark gray: pre-implementation, light gray: post-implementation group.

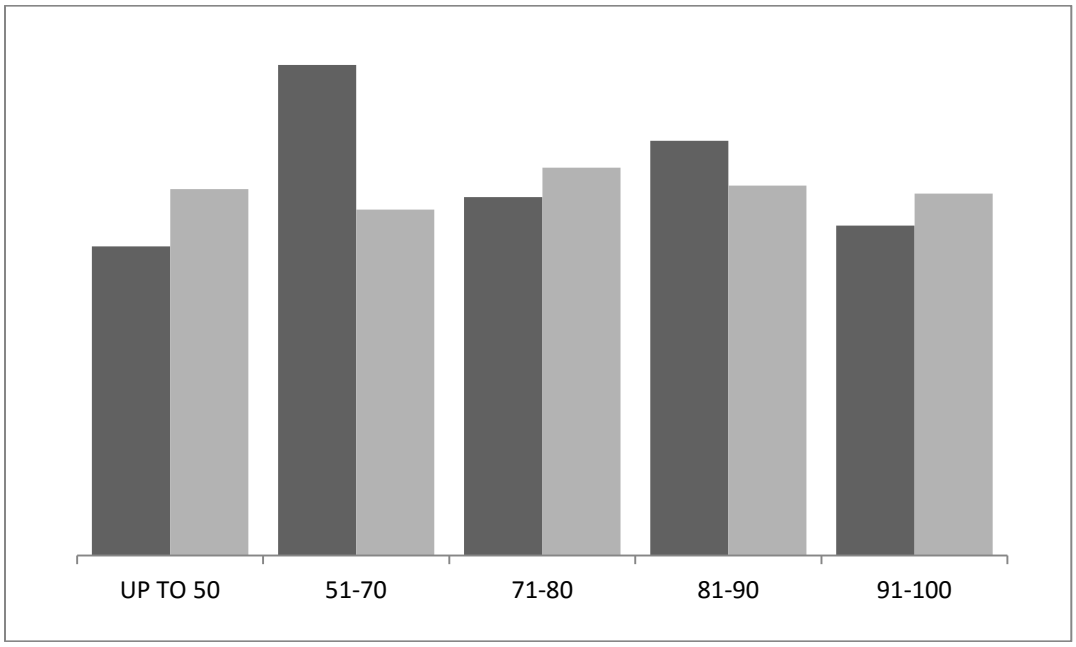


Figure M.2. LOS by Age and Group
*(Dark gray bar = pre-implementation group; light gray = post-implementation group).

Antibiotics Utilization

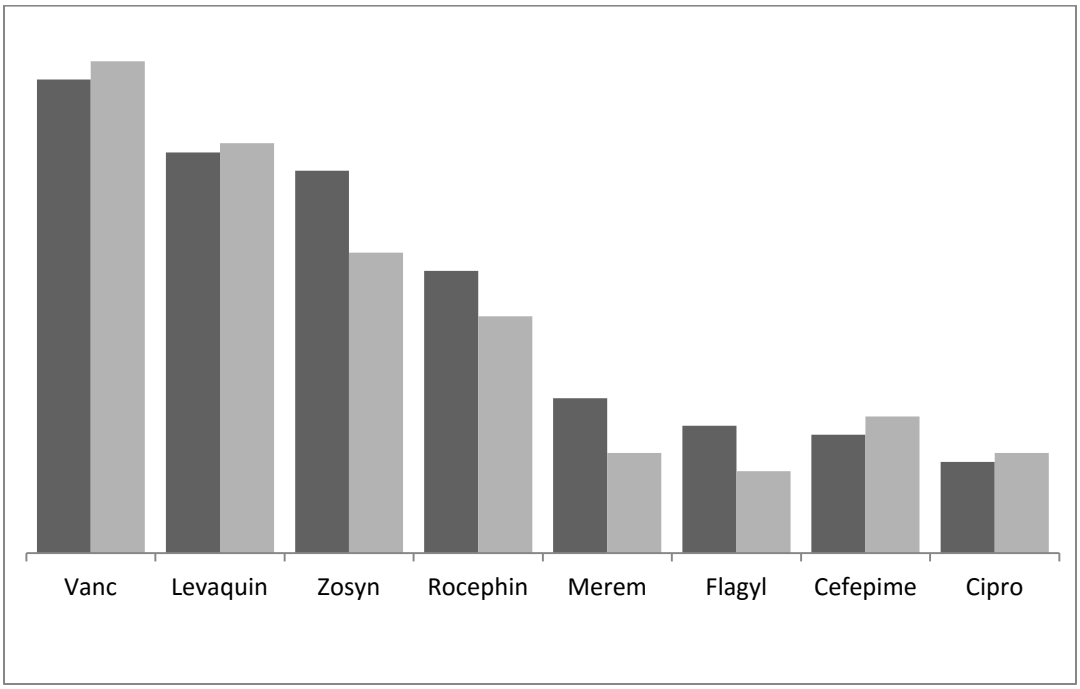


Figure M.3. Antibiotics Distribution
*(Dark gray bar = pre-implementation group; light gray = post-implementation group).

Table M.3. *Most Frequently Used Antibiotics*

Most Frequent Empiric Antibiotics used	**Pre (n=86)**	**Post (n=72)**
	%	%
Vancomycin	23.3	26.5
Levaquin	19.7	22.1
Zosyn	18.8	16.2
Rocephin	13.9	12.7
Cefepime	7.6	7.4
Cipro	6.3	5.4
Merem	5.8	5.4
Flagyl	4.5	4.4

Sepsis Associated Diseases and Causative Pathogens

Table M.4. *Sepsis Cause*

Sepsis Cause	Pre (n=86)	Post (n=72)
	%	%
Pneumonia	48	50
UTI	38	47
Bacteremia	22	35
GI/intraabdominal	21	11
Post-operative complications	10	3
Wound infection	9	10
Other	9	3
Neutropenic Fever	7	1
Skin (Cellulitis)	6	14
Pyelonephritis	5	7
FUO	3	3
Osteomyelitis	1	3
Meningitis	<1	1

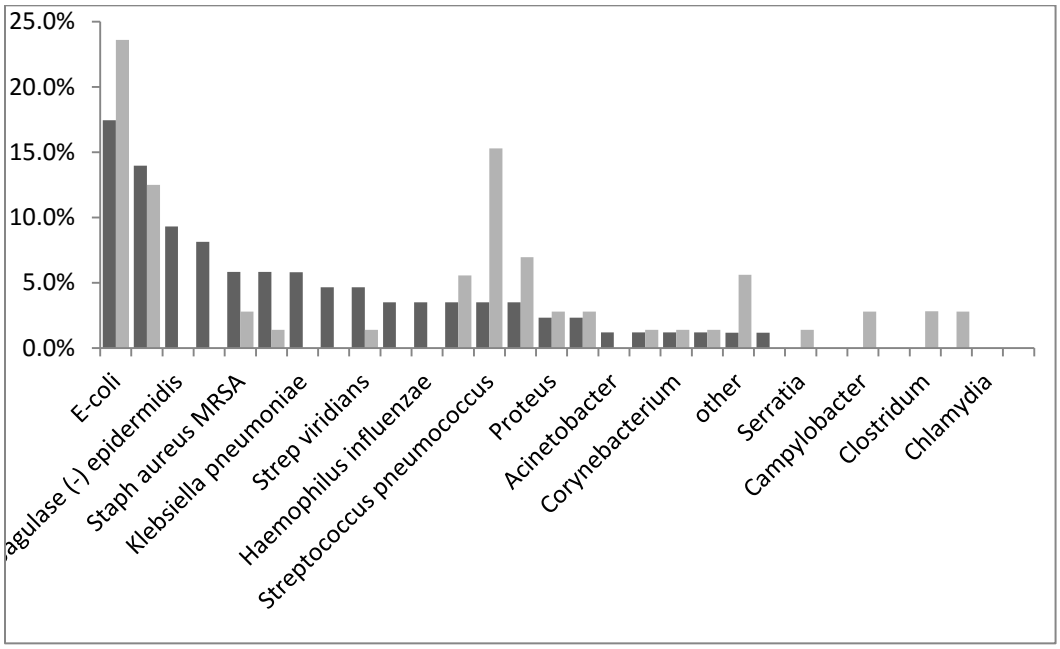


Figure M.4. Most Frequently Occurring Microorganisms Responsible for Sepsis.
*(Dark gray bar = pre-implementation group; light gray = post-implementation group)

Table M.5. *Most Frequently Occurring Pathogens*

Most Frequent Causative Pathogens Observed	**Pre (n=86)**	**Post (n=72)**
Pathogen	%	%
E-coli	17.4%	23.6%
Candida/Fungal	14.0%	12.5%
Staph coagulase (-) epidermidis	9.3%	0.0%
Enterococcus faecalis	8.1%	0.0%
Staph aureus MRSA	5.8%	2.8%
Viral (OthVir	5.8%	1.4%
Klebsiella pneumoniae	5.8%	0.0%
Pseudomonas aeruginosa	4.7%	0.0%
Strep viridians	4.7%	1.4%
Enterobacter	3.5%	0.0%
Haemophilus influenzae	3.5%	0.0%
Staph aureus MSSA	3.5%	5.6%
Streptococcus pneumococcus	3.5%	15.3%
other	3.5%	6.9%
Proteus	2.3%	2.8%
Enterococcus faecium	2.3%	2.8%
Acinetobacter	1.2%	0.0%
Strep group A pyrogens	1.2%	1.4%
Corynebacterium	1.2%	1.4%
Corynobacterium	1.2%	1.4%
other	1.2%	5.6%
Bacillus	1.2%	0.0%
Serratia	0%	1.4%
Morganella	0	0.0%
Campylobacter	0	2.8%
Neisseria	0	0.0%
Clostridum	0	2.8%
Mycoplasma	0	2.8%
Chlamydia	0	0.0%
Ricketts	0	0.0%
C-diff	2%	3%
MDR	17%	14%
All Sepsis w/ MRSA	10%	7%
MRSA cases among MDR associated with sepsis	60%	50%
ESBL	7%	10%
VRE	7%	0%

* E-coli: bacterium Escherichia coli; MRSA: resistant strain, Methicillin Resistant Staphylococcus aureus; MSSA: Methicilin Sensitive Staphylococcus aureus; C-diff: Clostridium difficile; MDR: multi-drug resistant organism.

Table M.6. *Legend for Data Collection:*

Code:	**Applies to:**
OutcMort	Outcomes, Mortality
OutcFS	Functional status at discharge
D/C	Discharge
ImDx	Associated diagnoses affecting immune status
Cmb	Comorbidities
IniPres	Initial presentation
AMS	Acute mental status change
SCs	Sepsis cause
Hcr	Hospital course
SpsPrgs	Progression of Sepsis
Abt<3h	Treatment with initial Antibiotics per protocol <3 hours from sepsis onset
AbtEmp#D	Number of days on empiric antibiotics
AbtEmp#	Number of empiric antibiotics prescribed
AbtDesc	Antibiotics Deescalated
AbtAppr	Appropriate antibiotic for diagnosis
IVF	Intravenous fluids per protocol at 30mL/hr and <3 hours from sepsis onset
LA1	Lactic Acid 1st drawn <3 hours from sepsis onset
LA1>2	Lactic Acid first sample results > 2
LA2_6h	Repeat Lactic Acid in 6 hours
Cult<3h	Blood cultures drawn prior to administration of antibiotic and <3 hours from sepsis onset
Cult#hrID	Number of hours pathogen group described or identified in a sample
Cult#hrFIN	Number of hours until final cultures results available, including MIC
CR	Culture results
C-diff	Clostridium difficile
P+	Site of positive cultures
Gn	Gram negative pathogen
G(+)	Gram positive pathogen
OthVir	Viral
OthFung	Fungal
MDR	Multi-drug resistant organisms
Ab	Antimicrobial class
OthTx	Other Treatment
AbtAppr	Appropriate antibiotic for culture results
HCaq	Healthcare Acquired infection
Cmp	Complications
Sav$LOS	Potential costs savings on length of stay
Sav$Abt	Potential costs savings on antibiotics de-escalation
Readm30	Readmitted within 30 days